EFFECTS OF BRIEF AND PROLONGED EMOTION ON COGNITIVE AND NEURAL PROCESSES ACROSS DEVELOPMENT

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Alexandra O. Cohen

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EFFECTS OF BRIEF AND PROLONGED EMOTION ON COGNITIVE AND NEURAL PROCESSES ACROSS DEVELOPMENT

Alexandra Ochoa Cohen, Ph.D.

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Emotional experiences are pervasive in everyday life and can influence our thoughts and actions. Dysregulation of cue triggered emotions and emotional mood states are core features of several mental illnesses, such as anxiety and mood disorders, that peak in prevalence during adolescence— a time of heightened sensitivity to social and emotional cues in the environment. During this period of development, emergence of exploratory and criminal behaviors is reflected in the “age-crime curve” whereby these behaviors emerge during the teen years and subsequently decline by the mid-twenties. Often when young people come in contact with the law, it is under emotionally charged situations, further highlighting the importance of understanding the impact of emotions on brain and behavior across development. We developed a novel behavioral paradigm for use with functional MRI to examine the impact of emotions on cognitive control and the neural circuitry. We incorporated brief and sustained positive and negative emotional states to distinguish effects of arousal versus valence.

We first tested for dissociable effects of both positive and negative emotional cues and states on cognitive performance and neural processes. We find that in adults, brief emotional triggers or cues, whether positive or negative, similarly influence cognitive control. In contrast, sustained emotional states

differentially impact cognitive control. Specifically, positive states enhance performance while negative state diminishes performance. Behavioral differences were paralleled by differential recruitment of fronto-parietal and fronto-striatal circuitry.

Central to our primary question, we next examined the impact of these emotions on behavior and brain during the transition from adolescence to adulthood, in teens 13 to 17, young adults 18 to 21, and over 21 years-old. We show protracted development of cognitive control in both brief and prolonged potentially threatening situations into the early twenties. This behavioral pattern was paralleled by developmental changes in prefrontal circuitry. The question remains as to how reactivity to emotional information during adolescence may impacts subsequent memory for this information. We show preliminary evidence that temporal dynamics of memory processes may be changing across development. Together these studies begin to dissociate complex influences of emotions on behavioral and neural processes across development and how they may differentially lead to changes in behavior and actions.

BIOGRAPHICAL SKETCH

Alexandra Cohen was born in Silver Spring and raised in Bethesda, Maryland. Her fondness for science began at young age, visiting her Abuelito's chemistry laboratory at the Pontifical Catholic University of Peru. She was inspired to study Neuroscience following her younger sister's diagnosis and operation of a benign brain tumor. She moved to Durham, North Carolina to study Neuroscience at Duke University. During her undergraduate years, she engaged in three formative research experiences—one at the National Institutes of Health and two at Duke University—each at different levels of analysis. Alexandra's experience at the National Institutes of Health motivated her to pursue her Ph.D. and the culmination of her research experiences lead to her desire to study developmental cognitive neuroscience. She learned of Dr. BJ Casey's pioneer status in applying neuroimaging techniques to the study of behavioral and brain development and aspired to earn her doctorate in Dr. Casey's lab at the Sackler Institute for Developmental Psychobiology at Weill Cornell Medical College. Dr. Casey's enthusiastic mentorship, constant guidance, and unwavering support were critical to the conception, execution, and completion of Alexandra's Ph.D. thesis.

This dissertation is dedicated to my amazing parents, Ana & Gary Cohen. Thank you for always helping me keep perspective, for picking me up when I stumble or fall, and for your ceaseless love and support. Any & every accomplishment of mine is thanks to you two.

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Chapter 1:

Adolescence: When social and affective inputs overshadow cognitive processes— An Introduction*

Adolescence is a typical developmental transition between childhood and adulthood, when the individual must learn to function relatively independent of the parent or caregiver. This developmental period is a time when the brain may be more “plastic” than it will ever be again, capable of remarkable adaptability in light of the many social, physical, sexual, and intellectual challenges encountered during this developmental phase (Casey et al., 2015). With these novel and multifaceted challenges comes the need for cognitive control – the ability to suppress irrelevant emotions, desires and actions in favor of adaptive or goal-oriented ones (Casey, 2015). During adolescence, the ability to exercise cognitive control is influenced by a heightened sensitivity to rewards (Galvan et al., 2006; Geier et al., 2010; Van Leijenhorst et al., 2010), potential threats (Cohen-Gilbert & Thomas, 2013; Dreyfuss et al., 2014; Grose-Fifer et al., 2013; Hare et al., 2008) and social inputs (Chein et al., 2010; Steinberg et al., 2009) in the environment. Gaps in knowledge remain as to when—during the course of development— and how—at both the behavioral and neurobiological levels— these social and emotional factors impact cognitive control processes. The present thesis aims to address these gaps in the extant literature in three experiments that investigate changes in

* The text and figures of this chapter has been taken in large part from a recently published book chapter (Cohen, A.O. and Casey, B.J. (2017). The Neurobiology of Adolescent Self Control. In T. Egner (Ed.) *The Wiley Handbook of Cognitive Control*). Edits were made for the purposes of tailoring the content to the current thesis, to include more recently published results, and to avoid repetition with content presented in subsequent chapters.

behavioral and neural correlates of cognitive control processes in both emotionally charged and relatively neutral situations. The overarching goal of this thesis is to better understand when and how cognitive control may be influenced by emotional inputs during the transition from adolescence to adulthood.

Development of Cognitive Control

Cognitive control is a theoretical construct at the heart of numerous theories of attention and memory (Baddeley, 1986; Cohen et al., 1992; Desimone & Duncan, 1995; Shallice, 1988) that has many different components (e.g., inhibitory control, performance monitoring, working memory) (Badre, 2011; Luna et al., 2015) and labels (e.g., "central executive," "attentional bias," “supervisory system”). These terms all suggest a mechanism that is required to inhibit reflexive actions (Shallice, 1988) and to redirect attention (Desimone & Duncan, 1995) and actions (Miller & Cohen, 2001) in favor of adaptive ones. Thus, cognitive control refers to a capacity to suppress irrelevant thoughts and actions, in favor of adaptive or goal-oriented ones (Allport, 1987; Casey et al. 2000, 2002; Cohen & Servan-Schreiber, 1992; Kahneman et al., 1983). Typically, when this ability involves the suppression of inappropriate emotions and desires, it is referred to as self control (Casey, 2015). The neural circuitry underlying control differs by the type of information and stage of processing being regulated or suppressed (Casey et al., 2000; 2005; Jonides & Nee, 2006). In other words, different circuitry may come into play when we suppress unwanted information by focusing attention on something else; suppress

unwanted thoughts by thinking about something else; or suppress an action, impulse or desire by engaging in an alternative action or withholding an action (Mischel et al., 2011; Casey et al., 2011).

Neuroimaging studies of cognitive control are consistent with this idea in that these studies show non-overlapping patterns of brain activity for a number of tasks including the Flanker, Go-Nogo, and Stroop tasks (Nee, Wager, & Jonides, 2007). These tasks and others that recruit cognitive control processes reveal modest, if any, correlations with one another in behavioral performance as well (Earles et al., 1997; Grant & Dagenbach, 2000; Kramer et al., 1994; Shilling et al., 2002; Tipper & Baylis, 1987). Together, these behavioral and neuroimaging findings suggest that control processes involved in resolving interference are likely due to multiple rather than a single mechanism, brain region or circuit. Nonetheless, lateral frontoparietal circuitry has been implicated reliably in imaging studies of cognitive control across a number of tasks (Vincent et al., 2008; Power et al., 2011).

Developmental studies of cognitive control processes such as suppressing unwanted information in memory in favor of relevant information (i.e., working memory) or suppressing an action in favor of an alternative one (i.e., response inhibition) show steady improvement during childhood that typically plateaus by adolescence (Casey, 2013; Davidson et al., 2006; Luna et al., 2010; Paus, 2005). The improvement in performance with age is paralleled by changes in patterns of activity in frontoparietal and frontostriatal circuitry across development (Adleman et al., 2002; Bunge et al., 2000; Casey et al., 1995, 1997; Crone et al., 2006; Darki & Klingberg, 2014; Durston et al., 2002, 2006;

Luna et al., 2001; Rubia et al., 2000; Tam et al., 2002; Thomas et al., 1999; Kwon et al., 2002; Rubia et al., 2006) and in white matter tracts within and across these circuits (Giedd et al., 2008; Liston et al 2006; Paus, 2005; Stevens et al., 2009), consistent with the basic circuitry implicated in adult neuroimaging studies of cognitive control. However, the development of cognitive control processes occurs in the context of significant reorganization of brain circuitry, especially during adolescence as structural and functional connections become more hardwired with maturation and experience (Casey, 2015; Casey et al., 2015).

Reorganization of the Brain during Adolescence

Cognitive, emotional and behavioral changes during adolescence are paralleled by hormonal and neurobiological changes that are regional in nature (Casey et al., 2015). Nonhuman primate and human postmortem studies show that this period is associated with regional elimination and stabilization of synapses that are predominantly excitatory (Huttenlocher & Dabholkar, 1997; Rakic et al., 1994). Sensorimotor regions undergo pruning before higher order association cortices. These regional changes in synaptic connections are paralleled by regional changes in patterns of cell firing and in the availability neurotrophins, neurochemicals, gonadal hormones and their receptors (Lee et al., 2014). For example, mesocorticolimbic dopamine and the endogenous cannabinoid system modulate regional changes in excitatory and inhibitory balance within cortical-subcortical circuitry (Doremus-Fitzwater & Spear, 2016; Floresco & Tse, 2007). Peaks in dopamine receptor expression within the accumbens (Brenhouse et al., 2008) occur before peak

dopamine signaling within the prefrontal cortex (Tseng & O'Donnell, 2007). Cannabinoid receptor and ligand levels are reported to be higher in the striatum and prefrontal cortex of adolescent relative to adult animals and activation of these receptors has been shown to modulate dopamine activity (Doremus-Fitzwater & Spear, 2016; Fitzgerald et al., 2012).

Human imaging studies reveal a similar pattern of regional changes in brain development with structural changes in phylogentically older sensorimotor cortex and subcortical limbic regions developing before association cortices, such as regions of the prefrontal cortex that do not reach maturity until the early twenties (Chugani et al., 1987; Gogtay et al., 2004; Mills et al., 2014; 2016; Sowell et al., 1999). Increases in white matter are concurrent with decreases in gray matter (Giedd et al., 1999; Giorgio et al., 2008; Simmonds et al., 2014), with association cortices showing the most pronounced changes in both myelination and cortical thinning throughout adolescence (Whitaker et al., 2016). Consistent with these neuroimaging findings, postmortem studies indicate that myelination in the human neocortex is protracted relative to nonhuman primates, continuing beyond adolescence, through the late twenties (Miller et al., 2012). The ubiquitous regional progressive and regressive changes in gray and white matter volumes and brain activity throughout the brain are thought to reflect refinement of functional circuits (Brown et al., 2005; 2006; Durston et al 2006).

Fundamental changes in patterns of functional connectivity throughout the brain have been shown across development using resting state functional MRI (rsfMRI). Early studies of rsfMRI revealed that over the course of

development, short-range, local functional connectivity decreases while long-range connections among brain regions increase (Fair et al., 2007; 2008; 2009). These findings suggest that there is a developmental shift towards integration of various brain networks into distributed functional networks with connectivity rapidly increasing with the onset of adolescence and plateauing by the mid-twenties (Dosenbach et al., 2010). Although more recent studies suggest that these results may be attributable in part to motion artifacts (Power et al., 2012), subsequent studies employing rigorous control for motion show smaller effects but similar results (Baker et al., 2015; Satterthwaite et al. 2012; 2013). Different functional networks also show differing developmental trajectories (Stevens, 2016) as indexed by changes in the balance of graph theoretical measures of within-network and between-network connectivity across development (Gu et al., 2015). Emerging research suggests that interactions between networks contribute to individual variability in cognitive control during adolescence (Dwyer et al., 2014). Together, these studies reveal that multiple functional networks, including frontoparietal and cingulo-opercular networks implicated in cognitive control processes (Power et al., 2011), all undergo reorganization from childhood to adulthood and may each provide unique contributions to the larger scale brain network architecture at different points in development (Gu et al., 2015; Stevens, 2016).

In the context of adolescent brain development, significant structural and functional changes occur in several limbic subcortical regions before higher order association cortices, including the prefrontal cortex (Galvan et al., 2006; Mills et al., 2014). These regional structural and functional changes have been hypothesized to lead to transient imbalances in functional brain circuitry that

can lead to dysregulation of emotions and actions during adolescence (Casey et al., 2008; Casey, 2015). Figure 1.1 highlights the development of a simplified neurocircuitry implicated in cognitive and affective control, from childhood to adulthood. Early work in rodents initiated the mapping of connectivity as well as unique and complimentary functions of each of these brain regions (Krettek & Price, 1977; Groenewegen & Berendse, 1990; Wright & Groenewegen, 1995).

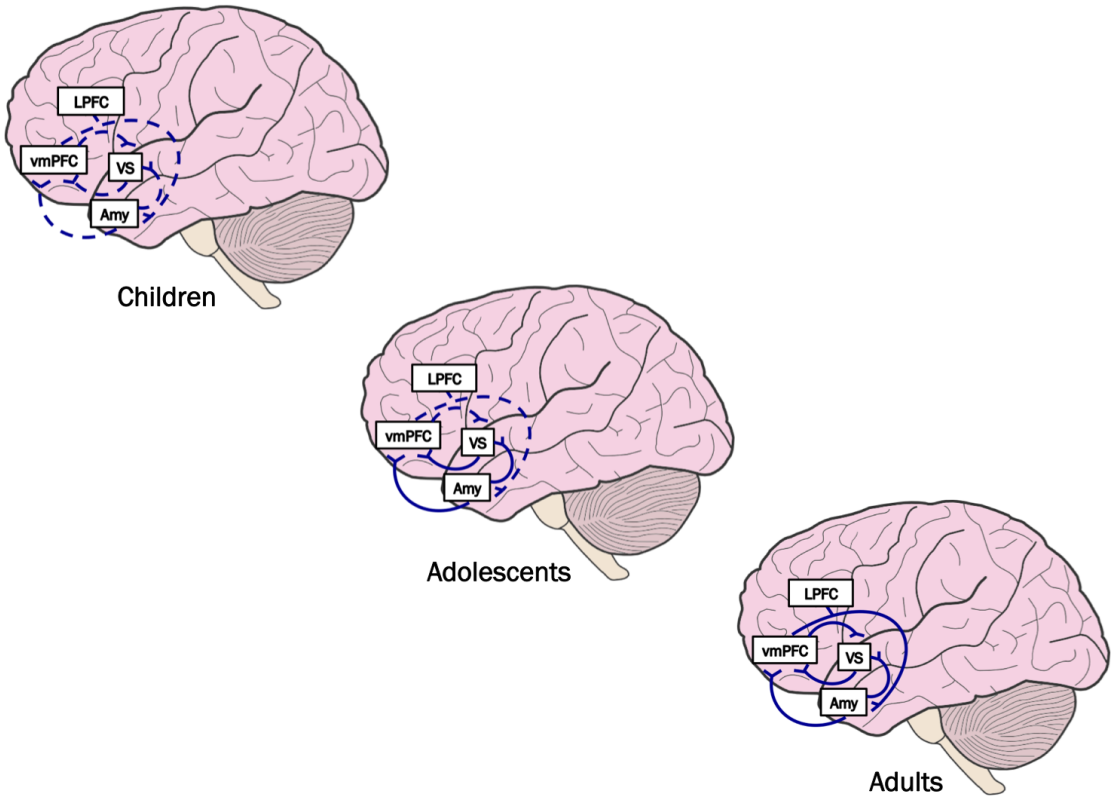

Figure 1.1: Schematic of cognitive and motivational circuitry development. The ventromedial prefrontal cortex (vmPFC) has reciprocal connections with both the amygdala (Amy) and ventral striatum (VS). The ventral striatum also receives direct projections from the basolateral amygdala. Subcortical connections from the amygdala to the ventral striatum are proposed to show changes before cortico-subcortical projections from prefrontal cortex. Subsequently, cortico-cortico connections from lateral prefrontal cortex (lPFC) to vmPFC implicated in cognitive control mature. Dotted lines represent immature projections.

Cross species research has implicated the prefrontal cortex broadly in behavioral regulation and the PFC can be roughly grouped into medial and lateral subdivisions. The medial PFC has reciprocal connections with both the amygdala and the ventral striatum and the lateral PFC projects directly to the amygdala and indirectly to the ventral striatum, with returning projections primarily going through medial PFC (Miller & Cohen, 2001; Tanji & Hoshi, 2008). The striatum, implicated in computations related to prediction of outcomes (Haber & Knutson, 2010), and the amygdala, a region involved in associative learning (Janak & Tye, 2015), are directly connected via ascending projections from the basolateral amygdala to the nucleus accumbens (Stuber et al., 2011). Considering these regions as interacting networks rather than unitary regions with orthogonal functions may drive developmental cognitive neuroscience research more toward a mechanistic understanding of why adolescents engage in the behaviors they do (Casey et al., 2015). Recent developmental neuroimaging studies have worked toward understanding the organization and function of these circuits by examining cognitive control in the context of motivational and socioemotional contexts (i.e. self control).

Motivational and Socioemotional Influences on Cognitive Control Development

The palette on which cognitive and neural development take place becomes more colorful and complex when we consider how emotional or motivational processes modulate or impact cognitive control processes, especially during adolescence. Socioemotional information is often present in contexts where individuals must exercise cognitive control (e.g. in the presence of rewards,

peers, or potential threats). Researchers have begun to provide a clearer picture of how recruitment of cognitive control changes across development by employing variations of simple behavioral paradigms, often in conjunction with neuroimaging, that incorporate these social and emotional elements.

Impact of Incentives. The influence of incentives on self control undergoes pronounced change from childhood to adulthood. Early work on how reward is functionally represented in the developing brain revealed that key components of reward circuitry—the ventral striatum and the orbitofrontal cortex— were sensitive to the magnitude of rewards (large vs small) across age groups (Galván et al. 2006). Adolescents show an exaggerated accumbens response to large rewards, relative to both children and adults, whereas the extent of orbitofrontal cortex activity exhibited more of a monotonic or linear pattern of change across development. Subsequent studies have shown differential accumbens activity in adolescents relative to adults in reward-related tasks (Bjork et al., 2008; 2010; Cohen et al., 2010; Geier et al., 2010; van den Bos et al., 2009). These findings and others have raised questions as to how incentives may exert influence over cognitive control during adolescence. For instance, an increased sensitivity to incentives could both diminish and enhance cognitive control in at least two ways. Motivational cues such as pictures of food, a smiling face or an accepting peer may capture attention and/or lead to impulsive actions toward that cue. In contrast, given the potential heightened sensitivity of rewards to adolescents, they may work harder and/or engage cognitive control more when receipt of reward is dependent on their actions (Geier et el 2010; Hardin et al., 2009; Teslovich et

al., 2014). We highlight work examining each of these potential outcomes of incentive sensitivity below.

A number of behavioral studies show marked performance differences across development when reward cues or incentives are used. Across these tasks, adolescents, as compared to adults, show increased risk taking when making decisions following immediate or positive reward outcomes as opposed to delayed ones (Figner et al., 2009; Cauffman et al., 2010). This increase in risky behavior appears to peak in mid to late adolescence. Delay discounting of reward values also varies with age, with younger adolescents showing a preference for smaller rewards sooner over larger rewards later, indicating diminished future orientation (Steinberg et al., 2009). Recent work shows that adolescents also demonstrate heightened tolerance to ambiguity and uncertainty, relative to children and adults, when making a risky decision (van den Bos & Hertwig, 2017). These studies suggest that both sensitivity to rewards and decreased weighting of potential outcomes peak during adolescence and that the salience of rewards may lead to breakdowns in performance on cognitive control tasks. An imaging study of a monetary gambling task revealed that increasing expected value of gambles more strongly influences gambling choices in adolescents than in adults (Barkley-Levenson & Galván, 2014). This behavioral effect was paralleled by increased ventral striatum activity in adolescents relative to adults, which remained pronounced even when the age groups were matched for performance, indicating that the neural developmental effect was likely due to a developmental difference in recruitment of reward circuitry.

In contrast to observations of appetitive cues diminishing cognitive control, heightened sensitivity to rewards during adolescence has also been shown to improve performance on cognitive control tasks. This phenomenon seems to be specific to circumstances when the rewards are contingent upon how well individuals perform. Variations of impulse control tasks like the antisaccade task, on which a participant must look in the opposite direction of a cue, have been used to test this. Adolescents showed enhanced performance relative to adults when instructed that the amount of money they could win was contingent on their performance on the task (Geier et al., 2010; Hardin et al., 2009). This improved performance was paralleled by increased ventral striatal activity in adolescents relative to adults when preparing to make a response in anticipation of a reward (Geier et al., 2010). Adolescents also showed increased activity in frontal eye field regions when preparing to make an eye movement, suggesting that rewards modulated or upregulated this control circuitry more in this age group than in adults.

Reward based perceptual discrimination tasks show similar results. When small and large rewards are paired with correct detection of the direction of moving dots, adolescents appear to be less impulsive as indexed by slower reaction times than adults for trials associated with the largest rewards. These slower reaction times may reflect that, when a large incentive is at stake, adolescents let evidence accumulate until they are confident in their choice before making a decision in order to maximize their gains. These behavioral findings are paralleled by ventral striatal activity on large reward trials across ages but enhanced recruitment of fronto-parietal control regions by adolescents relative to adults (Teslovich et al., 2014). Together these findings

suggest that adolescents' sensitivity to rewards is associated with changes in activation of striatal reward circuitry that influences the recruitment of cognitive control circuitry differentially from adults.

Influence of social cues and peers. During adolescence there is a heightened orientation and sensitivity to peer influences relative to either childhood or adulthood (Steinberg & Monahan, 2007; Guyer et al., 2012; Somerville et al., 2013). Social cues such as a simple smiling face can lead to impulsive behavior as measured on a go/nogo task in teens (Somerville et al., 2011). Specifically, when participants were told not to respond to rare smiling faces, only to neutral ones, adolescents were less able to withhold responses to the positive social cues as compared to both children and adults (Somerville et al., 2011). This impulsive, adolescent-specific behavior, was paralleled by increased ventral striatal activity in adolescents relative to children and adults (Figure 1.2). A functional connectivity analysis showed increased cortico-striatal coupling in adults, suggesting that immaturity of connections between

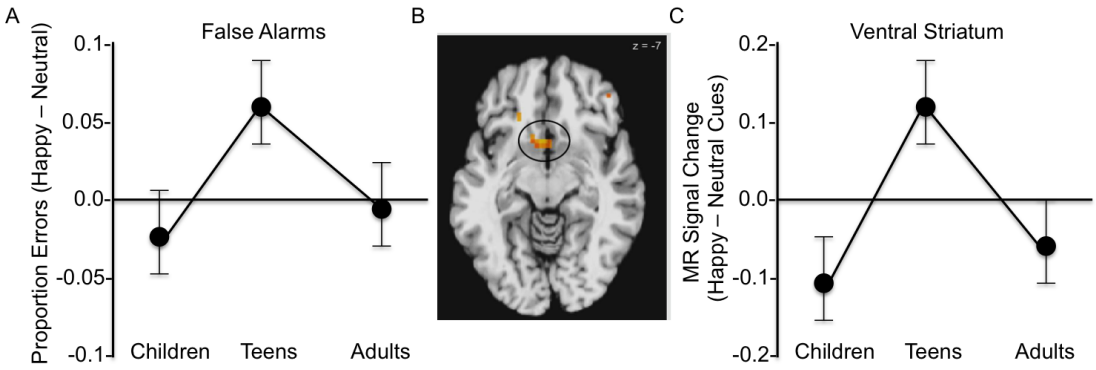

Figure 1.2: Sensitivity to positive social cues. Adolescents make more errors to rare happy face cues (A) relative to both children and young adults. This behavior is paralleled by increased ventral striatum (B) activity (C). From Casey, 2015; Adapted Somerville et al., 2011

control fronto-striatal circuitry and reward circuitry may underlie diminished cognitive control in response to positive social cues during adolescence.

Like positive social cues, the mere perceived presence of a peer can have a striking effect on cognitive control capabilities. Performance on decision-making tasks, such as deciding whether to drive through a yellow light at an intersection or not, show adolescent specific deterioration in performance when a peer is present versus when performing the task alone (Chein et al., 2011; Gardner &Steinberg, 2005; Weigard et al., 2014). This pattern of performance is paralleled by increased activation of brain areas implicated in reward circuitry, including the ventral striatum by adolescents, when choosing to go through the yellow light. The influence of peers on adolescent behavior is not specific to humans. Heightened sensitivity to peers is also observed in rodents. For example, “adolescent” mice consume more alcohol in the presence of another juvenile mouse than when alone, whereas adult mice show no difference in alcohol consumption with or without another mouse present (Logue et al., 2014). “Adolescent” rats show synergistic effects of drugs (nicotine and cocaine) and social stimuli such that interactions with other rats—even with limited physical contact (Peartree et al., 2012)—enhance conditioned place preference (Thiel et al., 2008; 2009). These findings suggest that the increase in risky behaviors when in the presence of peers during adolescence may be an evolutionarily conserved process across species.

Understanding how adolescents interpret and learn from social signals can provide insight into the observed shift in social sensitivity during this period. Jones and colleagues (2014) recently examined the effects of positive social

feedback on brain and behavior across development. Modeling trial-by-trial learning, children and adults showed higher positive learning rates than adolescents when receiving variable reinforcement from peers, suggesting that adolescents show less differentiation in their actions toward peers who provided more or less positive feedback. Forming expectations about receiving positive social reinforcement correlated with neural activity within the medial prefrontal cortex and ventral striatum across age. Adolescents, unlike children and adults, showed greater insular activity during positive prediction error learning and increased activity in the supplementary motor cortex and the putamen when receiving positive social feedback regardless of the expected outcome. These results suggest that peer approval may motivate adolescents toward action. While different amounts of positive social reinforcement enhanced learning in children and adults, all positive social reinforcement equally motivated adolescents. Together, these findings indicate that sensitivity to social stimuli during adolescence goes beyond simple reinforcement theory accounts and suggests possible explanations for how peers may motivate action in adolescents.

Influence of potential threat. Not all experiences during adolescence are positive. As the adolescent begins to negotiate the world on their own, without the protection of a caregiver, potential threats may arise. Cues that signal a potential threat or danger are believed to increase arousal and attention to prepare the organism for action (fight or flight). Life experiences with fearful facial expressions lead to the interpretation of these cues as signals of potential imminent danger in the environment (Ohman & Mineka, 2001). Such stimuli can lead to behavioral inhibition as measured by slower responses

times on cognitive tasks (Hare et al., 2005; Macleod, 1991; Simpson et al., 2000) and changes in psychophysiological responses, such as increased skin conductance and fluctuations in heart rate (Bradley et al., 2001; Ohman & Soares, 1998), consistent with the physiology of heightened arousal and increases in amygdala activity (Hare et al., 2005; Hariri et al., 2002; Scherf et al., 2013; Whalen et al., 2001).

Recent developmental studies suggest that the characteristic behavioral and neural responses to negative emotional stimuli shown in adults are altered during adolescence, a time when these socially relevant stimuli are particularly salient (Cohen-Gilbert & Thomas, 2013; Grose-Fifer et al., 2013; Monk et al., 2003). Adolescents, unlike children and adults, show more impulsive responses as measured by a Go/NoGo task when nontargets (letters) are superimposed on task-irrelevant negative scenes (Cohen-Gilbert & Thomas, 2013). They also show greater attentional capture by fearful faces when used as task-irrelevant flankers (i.e., greater interference effects, Grose-Fifer et al., 2013). These behavioral studies indicate that adolescents have difficulty suppressing attention and action towards cues of potential threat, even when the emotional cues are irrelevant to the task. Imaging studies parallel these findings, showing enhanced activity to fear faces in adolescents relative to adults (Baird et al 1999; Monk et al., 2003; Guyer et al., 2009) and children (Hare et al., 2008, see Figure 1.3). Activity in this region is positively correlated with reaction time, such that the greater the amygdala activity the slower reaction times in detection of these cues. Recently we examined the effect of threat cues on cognitive control. Adolescents were found to impulsively react to (i.e., approach rather than withdraw from) potential threat cues in a

Go/NoGo task more than children or adults (Dreyfuss et al., 2014). This adolescent specific peak in impulsivity to threat cues was paralleled by increased activity in medial prefrontal regions implicated in emotion regulation when successfully suppressing the impulse to respond to rare fearful faces cues, whereas greater lateral prefrontal activity, implicated in cognitive control, was associated with better behavioral performance across age. These results together with evidence of increased amygdala reactivity to emotional cues in adolescents (Hare et al., 2008; Guyer et al., 2009) suggest greater exertion of top-down regulation of subcortical structures may be necessary for effective recruitment of cognitive control circuitry in the presence of cues of potential danger.

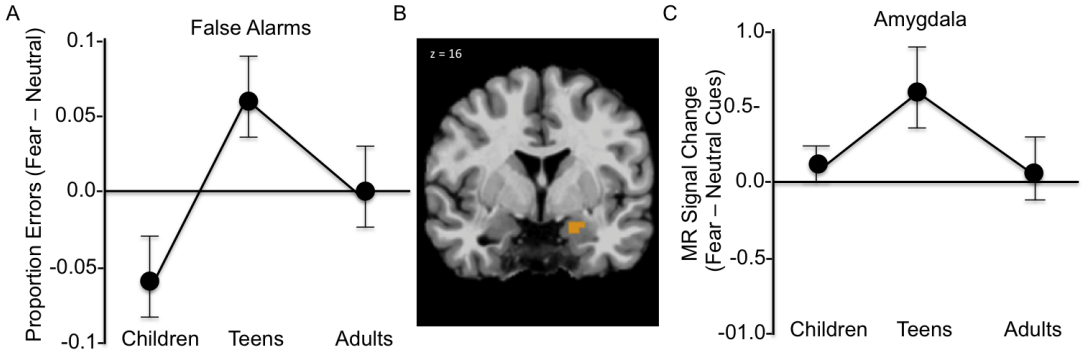

Figure 1.3: Sensitivity to cues of potential threat. Adolescents show greater false alarms (A) and amygdala (B) reactivity (C), relative to both children and adults, in response to fearful faces relative to neutral ones.
Adapted from Dreyfuss et al., 2014; Hare et al., 2008

Taken together, these studies of cognitive control suggest that adolescent reactivity to emotional cues and less mature cortico-subcortical circuitry may lead to less efficient modulation by lateral prefrontal control circuitry, resulting in diminished cognitive control capacity in emotional situations (Heller et al., 2016). These observations in humans are largely consistent with burgeoning work in “adolescent” animals that considers both the appetitive and aversive

properties inherent in most stimuli and how changes in neurobiology during adolescence may influence behaviors in response to stimuli in the environment. An adolescent phenotype of reward-centricity and attenuated responses to aversive properties of stimuli (Domerus-Fitzwater & Spear, 2016) has been proposed based on this work in rodents. Both the heightened sensitivity to rewarding and diminished sensitivity to aversive properties of stimuli may be evolutionarily conserved characteristics of adolescents that ultimately serve to motivate them towards action when faced with emotional situations. Although much of this research has thus far been behavioral, due in part to challenges in tailoring experiments for the short window of adolescence in rodents, recent work suggests that functional imbalances between cortical and subcortical circuitry are causally linked to deficits in inhibitory control (Meyer & Bucci, 2016). Future studies across development in both animals and humans will help to further elucidate the neural circuitry underlying the unique context-dependent patterns of behavior observed during adolescence.

Neurobiological Models of Adolescence

At least three prominent neurobiological models of adolescence have emerged over the past decade to explain the pronounced changes in cognitive control during this developmental period (Steinberg, 2005; Ernst et al 2006; Casey et al., 2008; Blakemore & Robbins, 2012, Figure 1.4 adapted from Casey, 2015). Of these, the dual system model has received the most attention, serving as a simple heuristic for linking brain and behavior. According to this model, there are orthogonal limbic “hot” and prefrontal “cold” systems that are in competition with one another (Metcalf & Mischel, 1999; McClure et al., 2004).

One analogy for characterizing these two systems builds on the 1960s television series *Star Trek* and its two main characters: James T. Kirk, the passionate captain of the *Starship Enterprise* from planet Earth who sometimes runs with his emotions and his first officer, Mr. Spock, a logical and rational native of the planet Vulcan. According to this analogy the cool prefrontal system is rational like Mr. Spock, while the hot limbic system is like the passionate Captain Kirk who has a tendency to ignore Starfleet regulations. This model provides a simple heuristic for how brain systems may compete, focusing largely on reward-based processes. Accordingly, the value-based dominance of the limbic system during adolescence is thought to result in diminished cognitive control and increased risky decision-making. With development of prefrontal cortex, the brain becomes more "vulcanized" which helps with the delay of gratification and more logical decisions (McClure et al., 2004; Cohen, 2005). Steinberg and colleagues suggest that during adolescence the cold system of the prefrontal cortex is less mature than the hot system and so the latter wins out when making decisions in motivated situations (among peers or rewards, Steinberg et al., 2008).

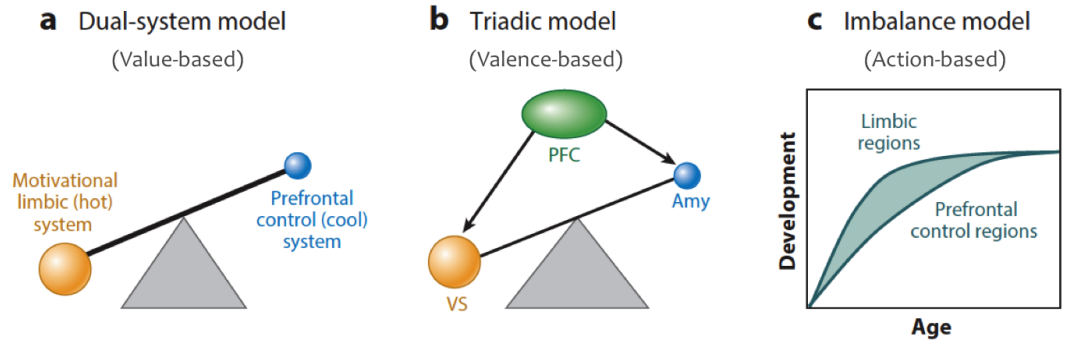

Figure 1.4: Neurobiological Models of Adolescence. Abbreviations: Amy, amygdala; PFC, prefrontal cortex; VS, ventral striatum.
Adapted from Casey, 2015

A second model proposed by Ernst and colleagues (2006; 2008) is the “triadic“ model. This model further subdivides the hot system from a reward system into both positively and negatively valenced subsystems that localize reward and threat to the ventral striatum and amygdala, respectively. The prefrontal cortex, serves as the modulator of these systems. Motivated behavior is proposed to stem from changes in gonadal hormonal and social reorientation that weight the reward system more heavily than threat during adolescence (Ernst et al., 2006; Ernst et al., 2008). This heavier weighting toward rewards over threats is thought to lead to thrill seeking and suboptimal choices during adolescence (Spielberg et al. 2014; Helfinstein & Casey, 2014). On the surface, thinking of adolescence as one big roller coaster ride of thrills seems tenable (Spielberger et al., 2014). However, converging animal (Paton et al., 2006), imaging (Delgado et al., 2008; Levita et al., 2009), and computational (Li et al., 2011) studies show that brain regions are not organized by valence. Amygdala activity has been observed to threat, but also in anticipation and receipt of rewards (Hommer et al., 2003), during presentation of happy faces (Somerville et al., 2004) and pleasant tones (Levita et al 2009). Likewise, the ventral striatum has been associated with reward processing (anticipation and receipt), but activity in this area has also been observed in response to social (Britton et al., 2006), novel (Rebec et al., 1997) and aversive stimuli (Levita et al., 2009). Both of these regions, the amygdala and ventral striatum, influence action in response to positive and negative outcomes (Schultz et al., 1997; O’Doherty et al., 2003; Roesch et al., 2010). This mounting evidence suggests that while it is important to understand neural responses to negatively and positively valenced cues, how we learn to respond to this information in the form of our actions (approach or avoid) may help to explain the diminished

capacity for cognitive control in their presence (Guitart-Masip et al., 2014; Huys et al., 2011).

A third model of adolescence is the imbalance model (Casey et al., 2008). This circuit-based model highlights *action* over *value* and *valence* in understanding adolescent behavior (Casey, 2015). We first proposed this model when finding regional functional brain changes within reward circuitry across development (Galvan et al., 2005; 2006). A nuance of this work was that adolescents not only showed differences from adults but also showed distinct behavior and brain activity from children (i.e., adolescent specific changes, Casey, 2013 for overview). The findings underscored that delayed prefrontal cortical maturation could not fully account for adolescent specific changes in behavior, because children have even less mature prefrontal circuitry. Instead, changes in behavior were posited to result from earlier functional changes in subcortical regions due to regional changes in synaptic pruning, peaks in available neurochemicals and increased local connectivity relative to prefrontal circuitry implicated in self control.

A subtle difference between the dual system and the imbalance model may be conceptualized best calling upon the *Star Trek* analogy again. Captain Kirk and Mr. Spock had a dynamic relationship on the Starship Enterprise. Mr. Spock interjected his logical reasoning on the bridge when the captain was being irrational or illogical in his behavior or decisions. There was no need to impose his logic when rational decisions were being made. Similarly, in development, there would be no need to strengthen connections between prefrontal and limbic regions if there were very little limbic activity. In fact, both

juvenile rodents and children show little subcortical limbic activity, specifically in the amygdala, in the presence of a parent, even in emotionally arousing situations, who serves to buffer and to regulate the child's emotions (Gee et al. 2014; Moriceau et al., 2006). During adolescence, this effect is not evidenced (Gee et al., 2014). Instead there appears to be an enhanced signal in the amygdala during this time (e.g., Gee et al., 2014; Hare et al 2008; Monk et al., 2003) that may help the adolescent learn to suppress their own emotions and actions by signaling the need for increased regulation by prefrontal circuitry. Signaling of prefrontal cortex could facilitate the hard wiring back from this region to inhibitory GABAergic cells within limbic structures, to enhance the capacity for regulation of emotions and actions within social bounds, and without the parent, in preparing for the adolescent for adult roles. This view of the adolescent brain underscores the need for circuit-level change within local and ascending connections of subcortical regions before distal descending prefrontal connections (see Figure 1.1).

More recently, work aiming to understand how cortico-subcortical connections help modulate this circuitry in cognitive control tasks has begun to emerge. We examined changes in task-based subcortico-subcortical and cortico-subcortical functional connectivity to emotional cues and the relationship of these functional connectivity changes to behavior across development (Heller et al., 2016). We find that amygdala-ventral striatum connectivity is inversely correlated with age and predictive of cognitive control performance, while increased medial prefrontal-amygdala connectivity is associated with better performance. Prefrontal-amygdala connectivity mediates the relationship between subcortical connectivity and cognitive control, suggesting distinct

roles for these circuitries in modulating cognitive control. This study, together with other emergent functional connectivity work (Baker et al., 2015; Silvers et al., 2016), suggest that between circuit modulation may be dependent on within circuit maturity (Casey, Cohen & Gee, submitted).

All of the proposed neurobiological models of adolescence underscore the importance of understanding the impact of social and emotional inputs on cognitive control during adolescence. Each model is in part consistent with the self control circuitry depicted in Figure 1.1. For the sake of simplicity, we illustrate these changes in these components of distributed functional networks across development in Figure 1.1 by placing emphasis on connections between lateral and medial prefrontal circuits later in development, often implicated in supporting cognitive and affective computations, respectively (Crone & Steinbeis, 2017). Functional connectivity between neural circuits is thought to be influenced by the relative maturity within each circuit (Dwyer et al., 2014; Baker et al., 2015; Silvers et al., 2016; van den Bos et al., 2009, 2012). Refinement of subcortical connections such as those from the amygdala to the ventral striatum that lead to motivated behavior (Heller et al., 2016; Stuber et al., 2011) are thought to mature before long-range cortico-subcortical projections such as those from the ventromedial PFC to GABAergic inhibitory neurons within the amygdala that help to modulate motivated and emotive behaviors (Gee et al., 2013). Subsequently, refinement of cortico-cortico connections within distributed functional networks occurs that help to modulate complex thoughts, emotions and actions.

Circuits or networks are the product of both experience and evolutionary-

based biological constraints (Karmiloff-Smith, 2009). Experiences help to shape the development of a network that can then be modulated by another network, which can in turn influence behavior and experiences (Byrge et al., 2014). Presumably the effectiveness of modulated networks relies upon maturation within a network and between networks, with within circuit development generally occurring before between network development (Dwyer et al., 2014; Baker et al., 2015; Silvers et al., 2016). Still, the relationships between the development of network connectivity and the development of cognitive and behavioral processes are still not well understood (Gu et al., 2015; Stevens, 2016).

While protracted developmental trajectories of cortical circuitry (Sowell et al., 1999; Miller et al., 2012; Mills et al., 2016) and adolescent specific sensitivities to social and emotional information (Steinberg, 2005; Ernst et al 2006; Casey et al., 2008; Blakemore & Robbins, 2012) have been observed across a large number of studies across species, it remains unclear exactly when and how cognitive control may be impacted by emotional inputs from the environment as functional neural circuitry continues to be refined into adulthood. An additional layer of intricacy has been added to these questions by a recently proposed model of adolescent neurobiology that highlights the influences of prior experiences and memory, via hippocampal circuit changes and alterations in mesolimbic dopamine availability, in modulating cognitive control throughout adolescence (Murty et al., 2016). There is presently little empirical work examining how emotion can impact learning and memory of events that may subsequently influence cognitive control behaviors across development. Understanding the complex influences of emotions on cognitive and neural

processes over the course of development may inform refinements to existing models of adolescent neurobiology and distinctions between typical and atypical patterns of behaviors that emerge during this transitional stage of development.

The Current Thesis

The goal of the current thesis is to examine the influence of both positive and negative brief and prolonged emotion on cognitive control and underlying neural circuitry across development. This dissertation research implements neuroimaging, psychophysiology, and two novel behavioral paradigms—one assessing cognitive control, the capacity to suppress attention and actions toward irrelevant competing information, the other memory processes, specifically working memory and subsequent recall memory—to investigate the multifaceted influences of emotions on cognitive and neural processes across development.

The format of the thesis is as follows: Chapter 1 "**Adolescence: When social and affective inputs overshadow cognitive processes– An Introduction**" provides an overview of the current understanding of the development of cognitive control and the influence of emotions on both the behavioral and neurobiological levels (adapted from Cohen & Casey, 2017). Chapter 2 "**The impact of emotional states on cognitive control circuitry and function**" (Cohen et al., 2016a) provides evidence for dissociable effects of positive and negative emotional cues and states on cognitive control and neural processes in healthy adults. Chapter 3 "**When is an adolescent an adult? Assessing**

cognitive control in emotional and non-emotional contexts" (Cohen et al., 2016b) examines the impact of both positive and negative emotional cues and states on cognitive control in the legally and socially relevant 18-21 age range, relative to younger and older age groups, and their underlying neural bases, based upon the paradigm described in Chapter 2. Chapter 4 "**The impact of emotional cues on memory processes across adolescence**" (Cohen et al., in prep) examines the effects of both positive and negative emotional content on subsequent memory from childhood through adulthood. The final chapter "**Conclusions and Implications: The complex influences of emotions on cognitive and neural processes across development**" provides a discussion that integrates the findings presented in the previous chapters, examines implications in the domains of mental health, legal, and social policy, and outlines future directions for this line of research.

Chapter 2:

The Impact of Emotional States on Cognitive Control Circuitry and Function*

Typically in the laboratory, cognitive and emotional processes are studied separately or as a stream of fleeting emotional stimuli embedded within a cognitive task. Yet in life, thoughts and actions often occur in more lasting emotional states of arousal. The current study examines the impact of emotions on actions using a novel behavioral paradigm and functional neuroimaging to assess cognitive control under sustained states of threat (anticipation of an aversive noise) and excitement (anticipation of winning money). Thirty-eight healthy adult participants were scanned while performing an emotional go/nogo task with positive (happy faces), negative (fearful faces) and neutral (calm faces) emotional cues, under threat or excitement. Cognitive control performance was enhanced during the excited state relative to a non-arousing control condition. This enhanced performance was paralleled by heightened activity of fronto-parietal and fronto-striatal circuitry. In contrast, under persistent threat, cognitive control was diminished when the valence of the emotional cue conflicted with the emotional state. Successful task performance in this conflicting emotional condition was associated with increased activity in the posterior cingulate cortex (PCC), a default mode network region implicated in complex processes such as processing emotions in the context of self and monitoring performance. This region showed positive coupling with fronto-parietal circuitry implicated in cognitive control, providing

* Cohen, A.O., Dellarco, D.V., Breiner, K., Helion, C., Heller, A.S., Rahdar., A., Pedersen, G., Chein, J., Dyke, J.P., Galvan, A., and Casey, B.J. (2016). The impact of emotional states on cognitive control circuitry and function. *Journal of Cognitive Neuroscience, 28(3),* 446-459.

support for a role of the PCC in mobilizing cognitive resources to improve performance. These findings suggest that emotional states of arousal differentially modulate cognitive control and point to the potential utility of this paradigm for understanding effects of situational and pathological states of arousal on behavior.

Introduction

Emotions are pervasive in our everyday life experiences, present in many decisions we make and actions we take. For example, how we react in traffic on our commute to work may vary by whether we just got cut off or just got let into moving traffic by another commuter. Although we each experience lability of emotional states in our daily lives, persistence of these emotions is a distinguishing feature of many psychopathologies (e.g., anxiety, depression, bipolar disorder; borderline personality) (Carpenter & Trull, 2013; Cisler et al., 2010; Gross & Jazaieri et al., 2014; Jazaieri et al., 2013; Joorman & Gotlib, 2010; Sheppes et al., 2015; Townsend & Altshuler, 2010). Understanding influences of emotional states on cognitive and neural processes may help elucidate emotional conditions and processes that alter typical and atypical behavior.

The interaction of emotion and cognition is typically examined by how well one can redirect attention from, or reappraise, emotional information presented in the form of brief emotional sounds, words, faces or pictures. These emotional stimuli are often embedded within well established cognitive control tasks like

the go/nogo (Hare et al., 2005), Stroop (Bush et al., 1998; 2000; George et al., 1994; Whalen et al., 1998; 2006), dot probe (MacLeod et al., 1986) and matching tasks (Vuilleumier et al., 2001; Bishop et al., 2004) to test for either interference or facilitation of attention and actions. Explicit instructions also may be given to reappraise emotional information as non-emotional or neutral (Heller et al., 2013; Ochsner & Gross, 2005; Wager et al., 2008). Successful redirection of attention from, or reappraisal of, emotional stimuli has been associated with cognitive control circuitry involving the prefrontal, parietal and anterior cingulate cortical regions (Ochsner & Gross, 2005; Wager et al., 2008), while focusing attention on this information has been associated with limbic brain regions (Buhle et al., 2014; Hartley & Phelps, 2010; Ochsner & Gross, 2005; Silvers et al., 2015; Wager et al., 2008). Fronto-parietal and fronto-striatal circuitry have been implicated broadly in cognitive control tasks (e.g. go/nogo, N-back, etc.) irrespective of the presence of emotional or motivational content (Owen et al., 2005; Simmonds et al., 2008; Vincent et al., 2008; Shackman et al., 2009). Taken together, these studies implicate these control systems in regulating emotional and motivational processes (Davidson et al., 2000; Hariri et al., 2000; Hare et al., 2005; Ochsner & Gross, 2005; Chiew & Braver, 2011; Buhle et al., 2014).

The previously described studies involve brief or momentary emotional stimuli rather than lasting emotional states of arousal. Emotion has also been examined across longer timescales in studies that induce an emotional state. For instance, mood induction studies use recollection of positive or negative autobiographical memories, guided imagery, film clips, or self-referential statements (Jallais & Gilet, 2010; Kohn et al., 2013; Wagner et al., 2012;

Westermann et al., 1996; Zhang et al., 2014) to engage and sustain an emotional state. Mood induction procedures have been shown to be relatively effective in inducing mood states but rely on subject control rather than experimental control, with variability among individuals (Kohn et al., 2013; Larcom & Isaacowitz, 2009). Other paradigms manipulate the uncertainty or timing of an outcome or event (Somerville et al., 2010; Alvarez et al., 2011; Somerville et al., 2013; Schlund et al., 2013) to induce periods of sustained anticipatory anxiety, as measured by self-report, psychophysiological, or imaging measures of mood and arousal. Few if any of these studies, however, have investigated how these sustained emotional states specifically impact cognitive control. Examining decision-making under emotional states of a longer timescale, with experimental control, may provide a more ecologically valid framework with which to understand the effects of real life emotional situations and/or pathological states of arousal on behavior.

The valence of emotional stimuli and states may differentially impact cognitive processes. A number of studies using discrete emotional stimuli have found that both appetitive and threat cues can interfere with cognitive control (Chiew & Braver, 2011; Hare et al., 2005; Hariri et al., 2000; Teslovich et al., 2014). Meanwhile, studies exploring the cognitive impacts of sustained emotional states have found differential effects dependent on the valence of the emotion. Specifically, positive mood states have been shown to broaden the scope of attention and improve cognitive performance in problem solving, memory recall, and decision-making (Ashby et al., 1999; Isen, 2000; Ashby et al., 2002; Frederickson & Branigan, 2005; Padmala & Pessoa, 2011) whereas, negative emotional states are associated with narrowing of attentional focus and

decreased cognitive capacity that results in diminished task performance (Easterbrook, 1959; Chajut & Algom, 2003; Frederickson & Branigan, 2005; Liston et al., 2009; Steenbergen et al., 2011).

The current study tests dissociable effects of both positive and negative emotional cues and sustained emotional states on cognitive control and neural processes within a variation of the emotional go/nogo task (Hare et al., 2005). Participants perform this task when "excited" about possibly winning up to $100 and when feeling "threatened" by the anticipation of an aversive sound. We hypothesized that negative and positive cues would similarly impact cognitive control capacity, while negative and positive mood states would differentially affect cognitive control (i.e., negative emotional states would diminish cognitive performance while positive emotional states would enhance performance). Likewise, we hypothesized that prefrontal and parietal control circuitry would be differentially modulated by sustained emotional states. We tested for dissociable differences in behavioral performance and brain activity to sustained emotional states and emotional cues and then explored interactive effects of emotional state and emotionally valenced cues on cognitive control.

Methods

Participants

Fifty healthy right-handed adults, ages 21 to 25 years, were scanned. Data from two participants were excluded due to poor overall performance (more than 2 standard deviations below the group's average performance as measured by d-prime). Data from four participants were excluded due to

excessive head motion (greater than 10% of time points censored as defined by >1.56 mm translational or 1 degree rotational motion within a run) and data from six participants were excluded due to technical problems. A total of 38 usable scans (18 males and 20 females; mean age = 23.61; SD = 1.34) are reported in the final analyses. Participants were recruited from a diverse community sample in New York City and Los Angeles as part of an on-going multisite project, and self identified as Caucasian (31.6%), African American (28.9%), Asian (23.7%), and Hispanic (15.8%). Participants reported no use of psychotropic medications or past diagnoses of, or treatment for, psychiatric or neurological disorders. All participants provided informed written consent approved by the Institutional Review Boards at both data collection sites.

Experimental Task

During the fMRI scan, participants completed a modified emotional go/nogo paradigm (Hare et al. 2005) that consisted of happy, fear and calm emotional expressions as both targets and nontargets (Figure 1A)—the Cognitive Control Under Emotion (CCUE) task. The task was performed under three emotional state conditions: while anticipating a negative event (threat), a positive event (excitement), or no event (neutral). Each condition was denoted with a distinctly colored background (Figure 1B). Participants practiced the task prior to entering the scanner to ensure that they understood the instructions and conditions.

The negative emotional state of threat (depicted on the blue background) was induced using verbal instruction of an unpredictable aversive auditory stimulus, previously used successfully in fear conditioning (Soliman et al.,

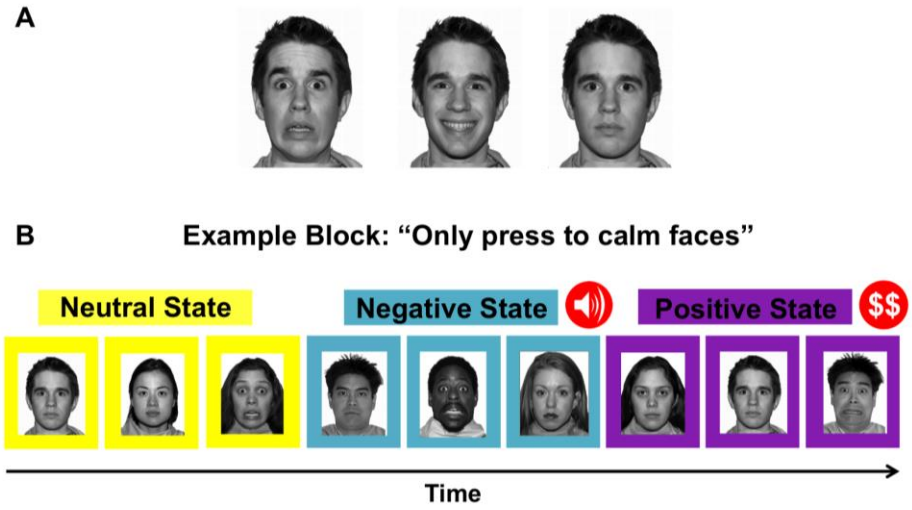

Figure 2.1: Experimental Paradigm. Examples of each facial type used in the paradigm: fear, happy, and calm (A). Schematic of one run of the emotional go/nogo imaging task with emotional cues as targets (go) or nontargets (nogo) (B). Cues occur within blocks of sustained negative emotion (unpredictable aversive noise), positive emotion (unpredictable reward), and neutral (no event), indicated by the background color of the screen (yellow, blue, or purple).

2010; Pattwell et al 2012), paired with an image representing a megaphone. The unpredictable nature of the potential to hear the noise maintains the sustained state of potential threat (Davis et al., 2010; Phelps et al., 2001). Verbal instruction of the possibility of winning up to $100 (depicted on the purple background) was used to induce a sustained positive emotional state of arousal (excitement) and was paired with the image and sound of a slot machine. Participants were instructed that the probability of an event occurring, the volume of the noise or the amount of money won, was not tied to their performance, but rather, was determined by the computer and would occur randomly, only when the background screen was the instructed color. In reality, participants heard the noise and won $20 exactly once over the course of the task, in a pseudorandomized order. The relevant event always occurred near the end of an experimental run so that the sustained emotional state

associated with anticipation of the event would have maximal duration, and so that TRs occurring subsequent to the event could be excised from analyses (to remove any potential artifact of the event). During a third state (depicted with a yellow background), participants were told there was no chance of any event occurring as they completed the task. Each state (75-second duration) occurred twice during each run.

Data were acquired in six 8-minute and 2-second runs representing each combination of emotional expression (calm, fear, happy) as a go or a nogo stimulus using a mixed block/event-related design. Run orders of the emotional go/nogo were pseudocounterbalanced and background color/emotional state pairings were counterbalanced. At the beginning of each run, participants were instructed which emotional expression was the target and reminded of the colored background/emotional state pairings. Participants answered a series of four questions to assure they were aware of each of these contingencies prior to the outset of each run. Participants were queried about the potential event associated with each of the three colored backgrounds in a yes/no format (e.g. “Does this color screen mean that you could win up to $100”) and were asked to confirm the target facial expression type (e.g. “Which face are you pushing for?”). Feedback was provided after each question, reiterating the contingencies. For each trial, a face appeared for 500 ms followed by a jittered intertrial interval (2-7 s). A total of 114 trials were presented in each run in a pseudorandomized order (84 go, 30 nogo across all cue types). In total, 60 nogo and 168 go trials, across all three cue types, were acquired for each emotional state for a total of 48 minutes and 12 seconds.

Behavioral and Psychophysiological Data Acquisition

Participants completed a final screening for MRI safety before being positioned in the scanner, with a 5-button (NY) or 4-button (LA) MR-compatible button box. The experimental task was presented using E-Prime 1.0 (NY) or 2.0 (LA) and was projected onto a flat screen mounted in the scanner bore. Participants viewed the screen via a mirror mounted on a 12-channel head coil. Skin conductance response (SCR) was acquired using disposable, isotonic gel electrodes, which were attached to the first and second fingers of the left hand between the first and second phalanges. The electrode cables were grounded through a RF filter panel. The skin conductance signal was recorded and amplified using a Biopac recording system and AcqKnowledge 4.0 (Biopac, Goleta, CA) software during fMRI scanning (200 Hz sampling). E-prime software was used to indicate the onset/offset of the emotional state during the task (Lim et al., 1997). SCR data were acquired from 48 of the 50 participants.

After exiting the scanner, participants were asked to answer debriefing questions about the believability of task conditions. Participants were asked how much they expected to win money or hear the noise during the block color that corresponded to the verbal instruction (e.g. “Did you expect to win money more during the purple blocks than the blue or yellow blocks?”). Each question consisted of a seven-point scale (1 = not at all; 7 = very much). Thirty-eight participants completed the post-scan questionnaire.

fMRI Data Acquisition

Whole brain fMRI data was acquired using Siemens Magnetom Trio 3.0 Tesla scanners located at the Citigroup Biomedical Imaging Center at Weill Cornell Medical College (WCMC) or at the University of California, Los Angeles. Scanning parameters were identical across data collection sites. A high resolution, T1 weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence scan was acquired using BIRN optimized sequences (Jovicich et al., 2006) (repetition time [TR] of 2170ms, echo time [TE] of 4.33 ms, 256-mm field of view [FOV], 160 slices, 1.0-mm x 1.0-mm x 1.2-mm sagittal slices). Functional images were acquired using T2*-sensitive echo planar pulse sequences covering the full brain. Thirty-eight 4-mm thick axial slices were acquired per 2500 ms TR (TE=30 ms; FOV=200-mm; Flip angle = 90°, 3.1 x 3.1 x 4.0 mm voxels).

Behavioral Data Analysis

Behavioral data were analyzed for accuracy using the sensitivity index d-prime that incorporates both accurate hits and false alarms (Macmillan & Creelman, 2004). D-prime was calculated by subtracting normalized false alarm rate from normalized go accuracy. Behavioral data, stimulus timing, and emotional state timing information were extracted and calculated using MATLAB and Statistics Toolbox Release 2013b. All statistical analyses were conducted using R (release 3.1.0). Main effects of emotional cue and state, and the emotional cue by state interaction, were analyzed using repeated measures analyses of the variance (ANOVAs) models controlling for sex and scanning site as between subject variables and with Bonferroni corrected post-hoc t-tests to determine statistical significance between conditions.

We examined responses to debriefing questions and SCR to assess the efficacy of our emotional state manipulation. A 1 Hz filter was applied to raw SCR data. Data was smoothed for each subject, and individuals with no discernable variation in SCR across runs were excluded, leaving 31 of the 48 participants in the analyses. SCR slope was extracted for each emotional state block within each run and was z-scored within each subject to account for individual differences in SCR. Slope values across each emotional state (excite, threat, and neutral) were then averaged. Change in skin conductance was computed as a difference scores between SCR slope values in an emotional state versus neutral. Given the directionality of our hypotheses with respect to these validation measures, one-tailed one sample Student's t-tests were performed to test whether debriefing questions were significantly different from one (the lowest value on the seven-point scale) and whether SCR differences were significantly different from zero.

fMRI Data Analysis

Image Processing. Functional imaging data were preprocessed and analyzed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). Preprocessing of functional scans included correction for slice time acquisition using sinc interpolation, volume registration using 6-parameter rigid-body transformation to account for head motion, and normalization to Montreal Neurological Institute (MNI) 152 1-mm T1 template using 12-parameter affine transformation and non-linear transformations (3dQWarp) were performed. Data were resampled to 3-mm isotropic voxels and were smoothed using a full-width at half maximum (FWHM) Gaussian kernel of 6-mm. Signal intensity of each voxel time series was normalized to percent signal change. Three

individual general linear models (GLM) were created for each participant to estimate separate aspects of the task: 1) Activation to emotional cues and sustained emotional states, 2) cue-state interactions, and 3) functional connectivity for the cue-state interactions.

Image Analysis. To disentangle the neural responses to the cues and to the sustained states, which were presented simultaneously, each participant's GLM included 16 regressors: Six task regressors consisting of correct responses to the emotional cues (fear, happy, and calm go trials and fear, happy and calm nogo trials). In the same model, three regressors were included to model the longer (30 TRs) sustained emotional states (i.e., the threat, excite and neutral sustained states). We also included a regressor corresponding to the incorrect trials (both go and nogo), as well six motion parameters. Baseline trends were estimated to capture shifts in signal change. Cues were modeled using a three parameter SPM gamma hemodynamic-response function (HRF); the sustained states were modeled using a single parameter block HRF. Time points with >1.56 mm (half voxel) of motion were censored as well as the preceding and following time points.

To examine cue-state interactions, a second GLM was run and consisted of 19 task regressors. In this GLM, each task regressor corresponded to the specific cue and sustained state. For example, the regressors incorporated information for each task and state (e.g., Threat-Calm-Go, Threat-Calm-Nogo, Threat-Happy-Go, Threat-Happy-Nogo, etc). Incorrect trials were modeled as a separate regressor, six motion regressors, motion censoring, and baseline

trend estimations were incorporated in this model, as in the previous model. Regressors were convolved with a three parameter SPM gamma HRF.

These individual level GLMs were submitted to group linear mixed-effects (LME) analyses using the AFNI 3dLME function (Chen et al., 2013), which is robust to small amounts of missing data. All group level analyses included a random intercept for each participant as well as sex and scanning site as between subject covariates. The first group level LME model assessed the main effect of the transient cues (the go as well as the nogo trials). The second group level LME model assessed the main effect of the sustained state (threat, excite, neutral). Lastly, given the observed behavioral interaction between emotional state and happy cue, a third group LME model directly paralleling the behavioral performance finding assessed the neural interaction of the sustained emotional state (threat and excite) with positive cue (happy). Group analyses were thresholded at $p < .05$ corrected for multiple comparisons using Monte Carlo simulation via the 3dClustSim program in AFNI. Individual subject regression coefficients were extracted from regions with significant main effects of emotional state and submitted to offline post-hoc analyses in R.

Psychophysiological Interaction Analysis. A generalized psychophysiological interaction (gPPI) analysis (McLaren et al., 2012; Cisler et al., 2014) was conducted in AFNI to examine task-dependent connectivity across the whole brain. The seed region was identified in the activation contrast of threat versus excite state to happy cue-- the posterior cingulate cortex. Briefly, the gPPI analysis was carried out by removing sources of noise and artifact,

deconvolving the neural signal, extracting the functional time course within the seed region (5-mm sphere around peak activation), and convolving the time course data with task timings and the canonical hemodynamic response function (McLaren et al., 2012; Cisler et al., 2014). The 19 task regressor individual GLM examining cue-state interactions, described above, was implemented, but for the gPPI analysis also included the seed time course and each time course/task interaction regressor for a total of 39 regressors plus the six motions regressors. Consistent with the analysis yielding the seed region, a group LME model, also controlling for sex and scanning site, was used to test the specific interaction of emotional state (threat and excite) with positive cue (happy). Group results for the threat state versus excitement state across target type contrast were thresholded at $p < 0.05$, corrected for multiple comparisons at the whole brain level using 3dClustSim, as described previously.

Results

Validation of Paradigm

To ensure that performance did not drop due to the long duration of the task, we examined differences in overall d-prime between the first and last run and found no significant differences in performance ($t_{(64.64)} = 0.13$, $p > 0.25$). We examined self-report measures and psychophysiology to assess the efficacy of the experimental manipulation. Self-reported responses to debriefing questionnaires and skin conductance response slope differences to emotional states were tested independently, so we used a Bonferroni adjusted alpha less than 0.025 to assess questionnaire response statistical significance and to assess change in SCR significance. Participants expected both the money

($t_{(38)}$ = 14.96, p < 0.0001) and loud noise ($t_{(38)}$ = 15.48, p < 0.0001) to occur during the instructed blocks (Figure 2A). Participants showed positive mean slope differences of SCR to both emotional states relative to neutral (Figure 2B). Although only the difference between the excite state and neutral was statistically significant ($t_{(30)}$ = 2.23, p = 0.016; threat – neutral, $t_{(30)}$ = 1.11, p = 0.14), SCR difference scores for the excite and threat conditions were not significantly different from each other ($t_{(30)}$ = 1.14, p = 0.26).

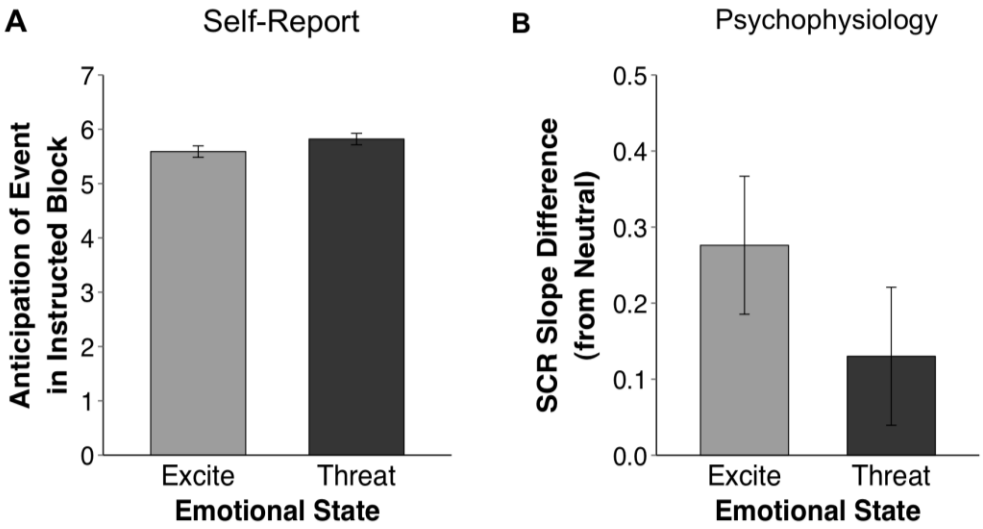

Figure 2.2: Validation of Paradigm. Participants expected to both win money and hear the loud noise during the instructed block (A). Participants also showed similar effects in skin conductance response in the emotional states relative to neutral (B). Means ± standard error (s.e.) presented.

Behavioral Results

To tease apart the effects of emotional cue versus emotional states on task performance, we examined d-prime to cues within the neutral state and d-prime to calm cues across emotional states. Repeated measures ANOVAs showed no main effect of cue type on performance ($F_{(2,74)}$ = 1.58, p = 0.21) (Figure 3A) but did reveal a main effect of emotional state ($F_{(2,74)}$ = 4.38, p =

0.016) (Figure 3B). Post-hoc bonferroni adjusted t-tests showed that this main effect was primarily driven by the difference between the state of excitement and neutral ($t_{(37)}$ = 2.87, p = 0.02; threat versus neutral $t_{(37)}$ = 1.59, p > 0.25; excite versus threat $t_{(37)}$= 1.39, p > 0.25). Assessing across all emotional cues and states, a two-way repeated measures ANOVA showed an emotional state by cue interaction ($F_{(4,148)}$ = 3.57, p = 0.008) (Figure 3C). The largest effect of emotional state appeared to be on performance to happy cues across the three emotional states of excite, threat, and neutral (Figure 5A). Thus, we submitted these data to post-hoc tests. Bonferroni adjusted t-tests revealed that participants showed enhanced performance to happy cues in the excite condition relative to neutral ($t_{(37)}$ = 3.05, p = 0.013), diminished performance in the threat condition relative to neutral ($t_{(37)}$ = 2.61, p = 0.039), and a pronounced difference in performance between excite and threat ($t_{(37)}$ = 6.29, p < 0.0001).

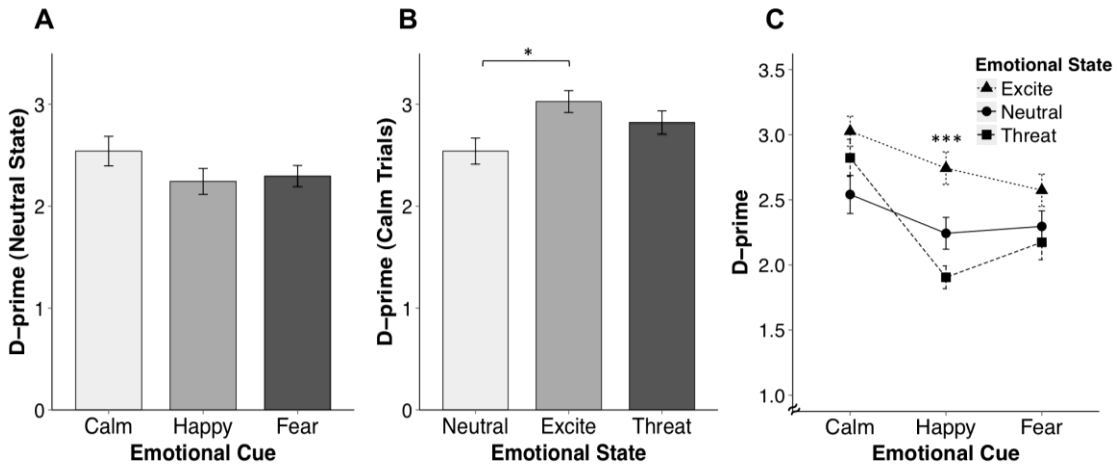

Figure 2.3: Sustained states of emotion influence performance to non-emotional and emotional cues. Behavioral performance dissociating emotional cue (A) from emotional state (B) and interactions between emotional states and cues (C). Means ± s.e. presented. * = p < 0.05, ***= p < 0.0001

Table 1. Response Type Activation Map (Go > NoGo)

Region	Brodmann's area	Peak Coordinate	Voxels, n	Z-stat
R Cerebellum		-14.5, +53.5, -20.5	384	+7.34
R Cerebellum		-14.5, +68.5, -47.5	50	+4.80
R Lingual Gyrus	18	-11.5, +98.5, -14.5	270	+4.68
R Cingulate	24	-11.5, -12.5, +33.5	79	-4.57
R Lateral PFC	3, 4, 6, 9	-44.5, +26.5, +63.5	359	-4.53
R Sup Temporal	22	-65.5, +38.5, +6.5	356	-4.53
R Precentral	6	-17.5, -9.5, +63.5	50	-4.33
R SMA	6	-14.5, +5.5, +69.5	31	-4.33
L Insula		+33.5, +2.5, -11.5	51	-4.26
L IFG	45	+27.5, -27.5, +0.5	38	-4.24
L Temporal Cortex	37	+39.5, +47.5, -11.5	44	-4.22
L Sup Temporal	22	+60.5, +59.5, +18.5	344	-4.21
L Cerebellum		+30.5, +68.5, -20.5	73	+4.17
L Precentral	6	+48.5, +2.5, +48.5	57	-4.15
L Insula		+30.5, -12.5, +6.5	36	-4.15
R Lateral PFC	10	-26.5, -48.5, +24.5	102	-4.13
L Precentral	4	+36.5, +26.5, +60.5	75	+4.12
R Mid Temporal	19	-35.5, +47.5, +0.5	28	-3.99
L Cingulate	24	+9.5, -3.5, +51.5	32	-3.88
R IFG	47	-41.5, -15.5, -2.5	29	-3.81
R Parietal	40	-41.5, +41.5, +42.5	27	-3.72

Cluster FWE corrected $p < 0.05$, individual voxel threshold 0.005, size ≥ 27 voxels

Imaging results

Main effects of emotional state and cue

Consistent with previous imaging studies using go/nogo tasks, in this variation we observed greater ipsilateral cerebellum ($Z = 7.34$, $p < 0.01$, corrected) and contralateral precentral gyrus ($Z = 4.12$, $p < 0.01$, corrected) activation to go trials relative to nogo trials and increased right ($Z = -3.81$, $p < 0.05$, corrected) and left ($Z = -4.15$, $p < 0.01$, corrected) inferior frontal gyrus (IFG) activation to nogo trials relative to go trials (Table 1). In studies implementing the emotional

go/nogo task across development, we have previously observed a correlation of right IFG BOLD signal change on nogo versus go trials and overall proportion of false alarms across ages (Somerville et al., 2011). In this sample of adult participants, we find a similar association ($r(36) = 0.31$, $p = 0.0549$) that was not observed for fronto-parietal regions ($r(36) = 0.199$, $p = 0.230$; parietal $r(36) = 0.255$, $p = 0.121$). In line with behavioral findings, no brain regions showed a main effect of cue that survived correction for multiple comparisons. The activation map for the main effect of emotional state revealed eleven regions showing differences in sustained activation (Table 2).

Table 2. Emotional State Main Effect Activation Map

Region	Brodmann's area	Peak Coordinate	Voxels, n	*F*-stat
R Parietal Cortex	40	-35.5, +56.5, +48.5	244	17.24
R dlPFC	9	-35.5, -36.5, +45.5	106	13.49
L Striatum		+9.5, -3.5, +3.5	92	12.02
R IFG/Insula	45, 13	-32.5, -21.5, +6.5	122	11.76
R Lateral PFC	10	-41.5, -51.5, +15.5	40	11.43
Middle Cingulate	23	-2.5, +23.5, +27.5	66	11.42
L Cerebellum		+6.5, +77.5, -29.5	65	10.80
Middle Cerebellum		-2.5, +53.5, -35.5	49	10.06
R dACC	32	-5.5, -27.5, +33.5	44	9.91
L IFG/Insula	47, 13	+36.5, -18.5, -2.5	34	9.68
R Caudate		-14.5, -3.5, +12.5	39	9.16

Cluster FWE corrected $p < 0.01$, individual voxel threshold 0.005, size ≥ 34 voxels

Given the behavioral findings of enhanced performance under a state of excitement, post-hoc tests were performed on the beta values extracted from

the four largest regions of activation, comparing activations between states using Bonferroni adjusted t-tests (Figure 4). These regions all showed relatively increased sustained activity in the excite state as compared to both the neutral and threat states: right parietal cortex (excite versus neutral $t_{(37)} = 4.55$, $p < 0.001$; excite versus threat $t_{(37)} = 4.73$, $p < 0.0001$; threat versus neutral $t_{(37)} = 0.18$, $p > 0.25$), right dorsolateral prefrontal cortex (excite versus neutral $t_{(37)} = 5.11$, $p < 0.0001$; excite versus threat $t_{(37)} = 3.93$, $p = 0.001$; threat versus neutral $t_{(37)} = 2.32$, $p = 0.077$), right inferior frontal gyrus and insula (excite versus neutral $t_{(37)} = 3.97$, $p < 0.001$; excite versus threat $t_{(37)} = 4.01$, $p < 0.001$; threat versus neutral $t_{(37)} = 0.06$, $p > 0.25$), and left striatum (excite versus neutral $t_{(37)} = 4.49$, $p < 0.001$; excite versus threat $t_{(37)} = 4.26$, $p < 0.001$; threat versus neutral $t_{(37)} = 0.43$, $p > 0.25$). Of these regions, only activation of the striatum was positively correlated with performance as measured by d-prime ($r(36) = 0.355$, $p = 0.029$). Sustained activity in this region was positively correlated with sustained activity in the prefrontal ($r(36) = 0.625$, $p < 0.0001$) and parietal regions ($r(36) = 0.446$, $p = 0.005$) during the excite state.

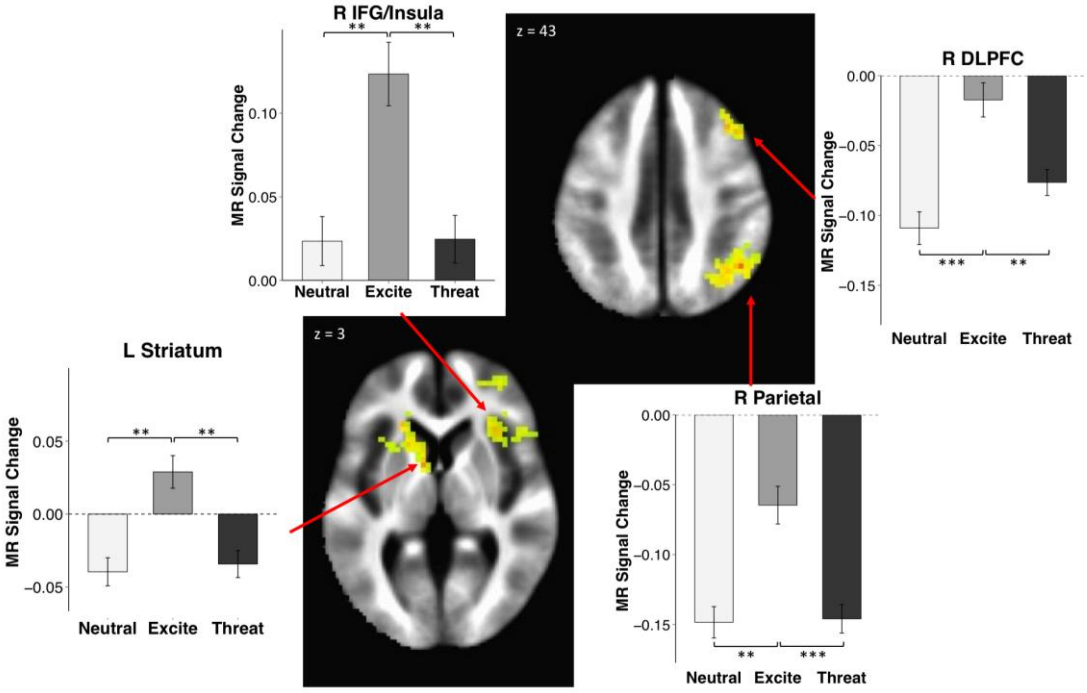

Figure 2.4: Heightened fronto-striatal and fronto-parietal activity under excitement. Representative axial images and extracted beta weights from regions showing a main effect of emotional state at $p < .01$, whole brain corrected. All brain regions show a similar pattern of increased sustained activation under a state of excitement relative to neutral and threat conditions. Means ± s.e. presented. **= $p < 0.001$, ***= $p < 0.0001$

Interactive Effects of Emotional State and Cue

We focused our analysis on the observed behavioral interaction between emotional cue and state (Figure 5A). Specifically, we compared BOLD signal to happy cues under threat versus under excitement. A single cluster survived whole brain correction, showing greater activation for the threat than excite state, in the posterior cingulate cortex (x = -11.5, y = 44.5, z = 27.5, $Z = 4.33$, cluster: 38 voxels, $p < 0.01$, corrected). PCC activation was enhanced when successfully engaging cognitive control on trials for which participants showed the most difficulty in performance.

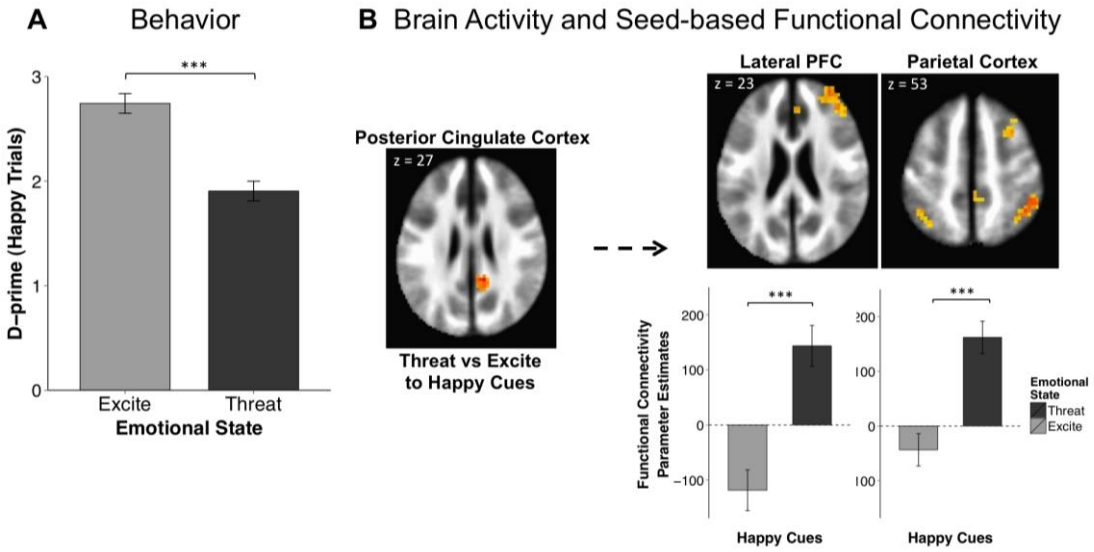

Figure 2.5: Diminished processing of positive information under threat. (A) Behavioral performance as indexed by d-prime to happy cues during states of excitement versus threat; (B) localization of brain activity in posterior cingulate cortex and seed-based functional connectivity with this region in dorsolateral prefrontal cortex and bilateral parietal cortex to happy cues during states of threat versus excitement. Means ± s.e. presented. **= $p < 0.001$, ***= $p < 0.0001$

A whole-brain generalized PPI analysis yielded seven clusters of voxels showing significantly greater functional connectivity with the PCC in the threat versus the excite condition to happy faces (see Table 3). Areas showing greater functional coupling included fronto-parietal regions (Figure 5B) as well as dorsal anterior and middle cingulate regions. Functional connectivity parameter estimates were extracted from the fronto-parietal clusters and post-hoc t-tests were performed on lateral prefrontal cortex ($t_{(37)} = 5.01$, $p < 0.0001$) and both parietal regions (right and left betas collapsed; $t_{(37)} = 4.91$, $p < 0.0001$). Functional connectivity parameter estimates did not show significant correlations with behavioral data. These findings show greater positive coupling between the posterior cingulate cortex and fronto-parietal control

circuitry when the emotional cue and emotional state are in conflict (i.e., a smiling face when under threat).

Table 3. PCC Functional Connectivity Activation Map (Threat > Excite to Happy Cues)

Region	Brodmann's area	Peak Coordinate	Voxels, n	Z-stat
R Parietal Cortex	40	-53.5, +44.5, +48.5	192	+5.31
R Middle Cingulate	31	-8.5, +29.5, +36.5	58	+5.28
R Lateral PFC	10	-35.5, -57.5, +21.5	134	+4.59
L Parietal Cortex	40	+48.5, +53.5, +39.5	49	+4.36
R Mid Frontal	6	-47.5, -0.5, +42.5	66	+4.12
R Lateral PFC	9	-53.5, -15.5, +39.5	42	+3.88
R dACC	32	-5.5, -36.5, +18.5	61	+3.81

Cluster FWE corrected $p < 0.01$, individual voxel threshold 0.005, size ≥ 34 voxels

Discussion

Emotional triggers and prolonged emotional states are believed to influence thoughts and actions, yet there has been relatively little investigation of how different emotional states directly influence cognitive control capacity and the underlying neural circuitry. The current study shows that, in healthy adults, brief presentations of emotional cues do not significantly enhance or diminish cognitive control capacity, whereas sustained states of emotion alter this capacity. Under sustained states of excitement, when participants thought they could win as much as $100 irrespective of their task performance, they showed enhanced cognitive performance. This finding is consistent with previous research suggesting that positive affect may broaden the scope of attention on cognitive tasks and improve performance (Ashby et al., 1999; Isen, 2000; Ashby et al., 2002; Frederickson & Branigan, 2005).

Improved performance under excitement was paralleled by increased sustained BOLD activation of fronto-parietal and fronto-striatal circuitry during this positive emotional state. Activation of these circuitries has been associated with performance in various cognitive control tasks (Owen et al., 2005; Liston et al., 2006; Simmonds et al., 2008; Vincent et al., 2008; Shackman et al., 2009; Buhle et al., 2014). Specifically, fronto-parietal circuitry has been implicated widely in cognitive control and attention processes, while fronto-striatal activity, including that in the inferior frontal gyrus, has been implicated more specifically in response inhibition (Hare et al., 2005; Liston et al., 2006; Vincent et al., 2008; Shackman et al., 2009; Heatherton & Wagner, 2011; Dodds et al., 2011; Aron et al., 2014; White et al., 2014). Activity in the striatum was positively correlated with performance and with activity in prefrontal and parietal regions. The sustained increase in recruitment of these circuits throughout the state of excitement together with enhanced performance is consistent with heightened representation of task demands (Miller & Cohen, 2001; Waskom et al., 2014) that in turn facilitates cognitive control capacity.

In contrast to the improvement in cognitive control under a positive state of excitement, this ability was diminished under sustained threat. However, this diminished capacity was dependent on the type of emotional information being processed. When the emotional cue conflicted with the emotional state (e.g., a smiling face under threat) behavioral performance declined. The presence of an emotional cue like a smiling face when under a state of potential threat is strikingly inconsistent with the negative emotional experience. This conflict at

the emotional level is not dissimilar from cognitive conflict observed when two cognitive inputs compete for attention, resulting in the need for more cognitive control (Botvinick et al., 1999; Casey et al., 2000). In the cognitive control literature, the anterior cingulate cortex has been implicated in resolving this form of conflict (Botvinick et al., 1999; Bush et al., 2000; Casey et al., 2000; Fan et al., 2008). In the current study, the conflict is between an emotional input and an emotional state. We show that this form of emotional conflict is associated with posterior cingulate cortex (PCC) activity.

The PCC is a major hub of the default mode network (DMN) that has been implicated in processing positive and negative affect in the context of self (Maddock et al., 2001; Maddock et al., 2003; Brewer et al., 2013). Non-human primate research has shown that the PCC has diffuse structural connections throughout the brain, including with other parts of cingulate cortex and association cortices in the frontal and parietal lobes (Parvizi et al., 2006; Leech & Sharp, 2013). Although there is still little consensus regarding the computational functions of the PCC (Leech & Sharp, 2013), evidence from nonhuman primate research suggests that the neuronal firing in the PCC is involved in complex processes such as performance monitoring and salience detection in motivated goal-directed cognition (Heilbronner et al., 2011; Pearson et al., 2011; Heilbronner & Platt, 2013; Leech & Sharp, 2013). It is hypothesized that a role of the default mode network may be to flexibly allocate cognitive resources in cognitively demanding situations in order to facilitate changes in behaviors that lead to successful task performance (Hayden et al., 2008; Pearson et al., 2009; 2011; Heilbronner et al., 2011; Leech et al., 2012; Heilbronner & Platt, 2013).

When the emotional cue conflicted with the negative emotional state the PCC showed positive coupling with fronto-parietal control circuitry. Consistent with the work in nonhuman primates, recent converging evidence in humans shows positive functional connectivity of default mode network hubs, including the PCC, with fronto-parietal networks when subjects are engaged in a goal-directed task. This heightened task-based connectivity is thought to represent the phenomenon proposed in nonhuman primate research of the PCC potentially mobilizing additional cognitive resources when necessary (Heilbronner & Platt, 2013; Leech et al., 2012; Pearson et al., 2011; Spreng et al., 2010). Thus, during this condition of conflicting emotional information, where participants are exhibiting the most difficulty performing the task, we observe relatively increased activity in the PCC and positive functional coupling with cingulate and fronto-parietal circuitry for correct trials. These results are consistent with a role for the PCC in mobilizing neural resources in cognitively taxing conditions.

An alternative interpretation of these data comes from the human resting-state fMRI literature. Studies of resting-state functional connectivity shed light on the functional organization and architecture of neural networks. Healthy subjects generally show negative connectivity, or inverse coupling, between DMN regions and task-relevant networks. Due in part to the high resting-state activity of DMN regions such as the PCC, it is thought that the commonly observed negative coupling is a reflection of redirecting attention outward from focusing inward on self (Uddin et al., 2009; Whitfield-Gabrieli & Ford, 2012; Leech & Sharp, 2013). Many psychiatric disorders characterized by cognitive

control problems show the opposite pattern of positive connectivity between default and control networks, including schizophrenia and depression (Whitfield-Gabrieli & Ford, 2012; Leech & Sharp, 2013). These alterations in resting state neural circuitry are thought to reflect components of the pathology, such as difficulties with redirection of attention and increased rumination. Thus, the heightened functional connectivity observed when emotional input and emotional state conflict in combination with diminished cognitive control is reminiscent of altered resting-state connectivity in psychiatric populations characterized by cognitive control problems.

Although simultaneous processing of conflicting negative and positive emotions diminished cognitive control capacity and elicited greater activity in the PCC for correct trials in the context of smiling faces under threat, the opposite pattern of behavior was shown when a fearful face occurred in the positive state of excitement. One potential explanation for this seemingly conflicting result is that fearful faces may be ambiguous stimuli that do not provide contextual information (Davis & Whalen, 2001). Several studies have suggested that positive or negative emotional context can bias the interpretation of ambiguous facial expressions (Kim et al., 2004; Neta et al., 2011). In the present study, the prevailing positive emotional context (anticipation of winning money) may influence the interpretation of ambiguous stimuli such as a fearful face as surprise rather than threat thus reducing the degree of conflict in the different forms of emotional information. Specifically, performance was enhanced to fearful relative to neutral faces in the positive emotional state. This interpretation is consistent with general improvements in cognition when experiencing positive affect (Ashby et al., 1999; Isen, 2000;

Ashby et al., 2002; Frederickson & Branigan, 2005).

While healthy adults show diminished performance and differential recruitment of task-related circuitry when faced with conflicting emotional information, it is still unclear how competing emotional inputs may differentially influence cognitive control and neural processes in different conditions, such as in developmental or psychiatric populations. Adolescence is a time of heightened sensitivity to emotional and social inputs (Casey, 2015), thus understanding complex influences of emotions on cognitive and neural processes during this typical stage of development may provide further insights into situational effects on behavior. Furthermore, emotional problems are hallmarks of a wide range of psychopathologies (Carpenter & Trull, 2013; Cisler et al., 2010; Joorman & Gotlib, 2010; Townsend & Altshuler, 2010) that peak during this developmental period with one in five adolescents meeting criteria for a mental illness (Kessler et al., 2005; Merikangas et al., 2010) highlighting the importance of developmental considerations in this line of research (Lee et al., 2014; Casey et al 2015). The influence of emotions on cognitive and neural processes in developmental and psychiatric populations is a primary area of empirical investigation and one that may have important implications for clinical assessment and interventions that may improve outcomes (Davidson et al., 2002; Gross & Jazaieri, 2014; Lee et al., 2014; Sheppes et al., 2015). The behavioral paradigm reported in the present study may be useful in probing the complex interactions between cognition and emotion in developmental and psychiatric populations.

The findings reported here must be considered in light of their limitations. We

here refer to the sustained states of positive arousal and negative arousal as “excitement” and “threat”, respectively. However, we do not have a measure of these mood states to directly assess how the participants were feeling. Additionally, although we observed significantly increased skin conductance across the excite state relative to neutral, the increase in skin conductance in the threat state relative to neutral was not significantly different from zero. Much of the SCR data collected was not usable and there was significant variability in the data. Data may have been particularly noisy because it was acquired in the scanner and because subjects viewed brief emotional cues throughout each state block. Examining SCR data in a larger sample may help to increase power and reduce noise. It is also possible that some participants did not find the loud noise as aversive as others did although this stimulus has been validated as aversive in previous imaging research (Levita et al., 2009; Soliman et al., 2010). Investigating individual differences in responses to these induced emotional states may yield further insight into how emotion differentially impacts cognitive control among individuals.

The present study implements a novel neuroimaging paradigm for examining how emotional information and states impact attention and actions, for better or worse. We demonstrate that emotional states and cues have dissociable and interacting influences on cognitive control processes and on the underlying neural circuitry. Our findings suggest that sustained positive states are associated with improvements in performance in healthy adults, while conflicting positive emotional information under a negative state diminishes performance and alters neural activation and connectivity. Understanding complex influences of emotions on cognitive and neural processes in healthy

participants is a first step toward delineating conditions (e.g., pathological, developmental or environmental) for which emotional processes may alter behavior.

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Chapter 3:

When Is an Adolescent an Adult? Assessing Cognitive Control in Emotional and Nonemotional Contexts*

An individual is typically considered an adult at age 18, although the age of adulthood varies for different legal and social policies. A key question is how cognitive capacities relevant to these policies change with development. The current study used an emotional go/no-go paradigm and functional neuroimaging to assess cognitive control under sustained states of negative and positive arousal in a community sample of one hundred ten 13- to 25-year-olds from New York City and Los Angeles. The results showed diminished cognitive performance under brief and prolonged negative emotional arousal in 18- to 21-year-olds relative to adults over 21. This reduction in performance was paralleled by decreased activity in fronto-parietal circuitry, implicated in cognitive control, and increased sustained activity in the ventromedial prefrontal cortex, involved in emotional processes. The findings suggest a developmental shift in cognitive capacity in emotional situations that coincides with dynamic changes in prefrontal circuitry. These findings may inform age-related social policies.

* Cohen, A.O., Breiner, K., Steinberg, L., Bonnie, R.J., Scott, E.S., Taylor-Thompson, K.A., Rudolph, M.D., Chein, J., Richeson, J.A, Heller, A.S., Silverman, M.R., Dellarco, D.V., Fair, D.A., Galvan, A., and Casey, B.J. (2016). When is an adolescent an adult? Assessing cognitive control in emotional and non-emotional contexts. *Psychological Science, 27(4),* 549 – 562.

Introduction

Definitions of adulthood in the United States differ according to state law and policy. Although most states set the age of majority at 18, the legal age for purchasing alcohol is 21 (Institute of Medicine & National Research Council, 2014), and the minimum age for criminal prosecution is 14 or younger in most states (Taylor-Thompson, 2014). In scientific studies, 18 is often used as the cutoff for adulthood even though government research policies, until recently, considered individuals under 21 to be minors. Thus, the legal definition of adulthood is fluid and imprecise. One consideration in defining adulthood is when behavior, and the underlying neural circuitry, can be said to have reached maturity. Extant studies suggest that this may vary depending on the context in which adolescents are assessed. In the current study, we compared the development of cognitive control in neutral and emotionally arousing situations because the latter seem highly relevant to many policies relating to definitions of adulthood.

Although a large developmental literature shows that adolescents' speed and accuracy on simple cognitive tasks can resemble adults' (Luna, Marek, Larsen, Tervo-Clemmens, & Chahal, 2015), mounting evidence suggests that contextual factors influence performance differentially as a function of age. Studies show that adolescence, typically defined as ages 13 through 17, is a time of heightened sensitivity to motivational, social, and emotional information (Casey, 2015; Steinberg, 2010). Specifically, during adolescence, cognitive-control capacities and decision making appear to be especially influenced by incentives (Galvan et al., 2006; Geier, Terwilliger, Teslovich, Velanova, &

Luna, 2010; Somerville, Hare, & Casey, 2011; Van Leijenhorst et al., 2010), threats (Cohen-Gilbert & Thomas, 2013; Dreyfuss et al., 2014; Grose-Fifer, Rodrigues, Hoover, & Zottoli, 2013; Hare et al., 2008), and peers (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011; Gardner & Steinberg, 2005). Behavioral regulation in response to these inputs has been shown to rely on prefrontal circuitry (Dreyfuss et al., 2014; Hare et al., 2008; Somerville et al., 2011), which shows marked change into the early 20s (Gogtay et al., 2004; Sowell et al., 2004).

Prominent neurobiological theories of adolescence suggest that dynamic and asymmetric trajectories in structural and functional development of limbic and prefrontal circuitry are implicated in motivated behavior and its control, respectively, and may lead to a propensity toward risky and impulsive actions (Casey, 2015; Casey, Getz, & Galvan, 2008; Ernst, Pine, & Hardin, 2006; Mills, Goddings, Clasen, Giedd, & Blakemore, 2014; Steinberg, 2010). Phylogenetically older brain regions, such as subcortical limbic regions, show nonlinear developmental changes and appear to be functionally sensitized during adolescence (Galvan et al., 2006; Hare et al., 2008; Raznahan et al., 2014), whereas development of prefrontal cortex (PFC) exhibits a roughly linear trajectory (Galvan et al., 2006; Gogtay et al., 2004; Sowell et al., 2004). Resting-state functional connectivity data show prolonged development of long-range cortical connectivity that does not stabilize until the 20s (Dosenbach et al., 2011; Fair et al., 2009). Together, these results suggest continued refinement of brain circuitry, particularly prefrontal cortical circuitry, into young adulthood, but the behavioral implications of this protracted brain development remain unclear.

The current study compared the development of cognitive control under brief and prolonged states of emotional arousal and nonemotional states. We focused on the 18-to-21 age range given the protracted development of prefrontal circuitry and the particular legal and social relevance of this age group. Our key premise was that responses in emotional situations would provide insight on cognitive capacities relevant to social and legal policy, such as those related to criminal responsibility and accountability. Prior research examining motivational and social influences on cognitive capacities in young adults has used varying age ranges and experimental manipulations that have produced mixed results (Chein et al., 2011; Cohen-Gilbert et al., 2014; Silva, Shulman, Chein, & Steinberg, 2015; Steinberg et al., 2009). We attempted to control for several of these variables by testing the impact of both brief and sustained positive and negative emotional states on cognitive control, using predefined age groups as well as age as a continuous variable. We hypothesized that there would be a developmental shift in cognitive control in emotional situations that would correspond to dynamic changes in prefrontal circuitry. Specifically, we predicted that young adults 18 to 21 years old would differ from adults over age 21 in cognitive control in emotionally arousing conditions (as teens do) but not in neutral conditions.

Method

Participants

Participants were 110 individuals from a larger sample of 147 healthy, right-handed 13- to 25-year-olds who underwent functional MRI (fMRI) while performing an adapted emotional go/no-go task (Hare et al., 2008) under

sustained emotional states of threat and excitement and under nonemotional states (Cohen et al., in press). Data from 5 participants were excluded because of their poor overall performance (> 2 *SD* below the group's average performance as measured by *d*′). Data from 14 participants were excluded because of excessive head motion (more than 10% of time points within a run censored because of translational motion > 1.56 mm, or half a voxel, or rotational motion > 1°), and data from 18 participants were excluded because of technical problems that led to errors in coding and recording of behavioral data in the scanner. A total of 110 usable scans were included in the final analyses reported here (41 teens—23 females and 18 males, ages 13–17 years, *M* = 16.19, *SD* = 1.20; 35 young adults—17 females and 18 males, ages 18–21 years, *M* = 19.88, *SD* = 1.09; 34 adults—17 females and 17 males, ages 22–25 years, *M* = 24.08, *SD* = 1.04). Portions of the data from 38 adults in this sample are included in a separate report (Cohen et al., in press) focusing on different experimental questions.

Participants were a diverse community sample recruited from New York City and Los Angeles as part of an ongoing multisite project. They self-identified as Caucasian (32.7%), African American (27.3%), Hispanic (24.6%), Asian (12.7%) and "other" (2.7%). The recruitment target for this portion of the study was 125 participants, in anticipation of 20% attrition due to excessive head motion, poor performance, or technical issues. Because of exclusions due to poor task performance and technical issues in the scanner environment, 22 additional participants were run. Participants reported no use of psychotropic medications or past diagnoses of or treatment for psychiatric or neurological disorders. Adults and parents provided informed written consent, and minors

provided assent. The institutional review board at each site approved the study.

Experimental task

Participants completed a modified emotional go/no-go paradigm (Hare et al., 2008) called the Cognitive Control Under Emotion (CCUE) task (Cohen et al., in press). In this task, happy, fearful, and calm emotional expressions (Fig. 1a) are presented as targets, which participants are instructed to respond to (go trials), and nontargets, which participants are instructed not to respond to (no-go trials). The task is performed in blocks of sustained anticipation of a negative event (aversive sound), a positive event (winning up to $100), and no event; each type of block is denoted with a different background color on the

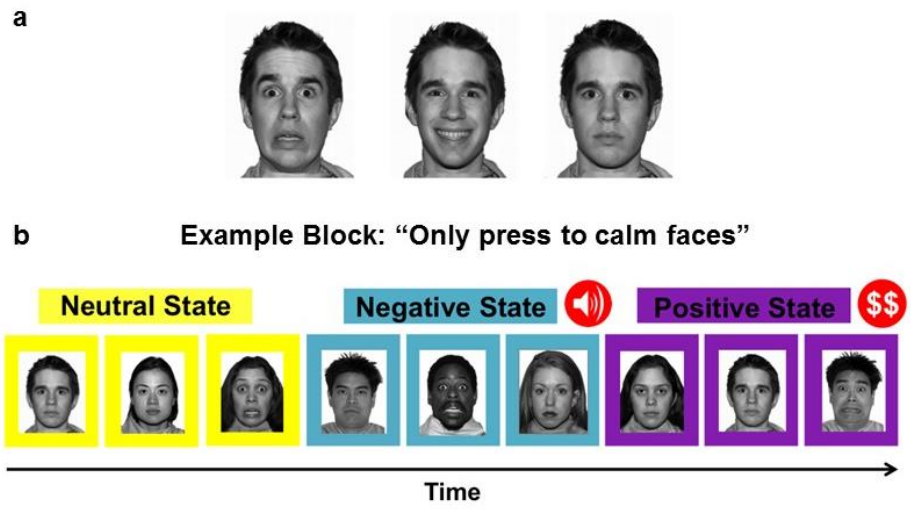

Figure 3.1: The Cognitive Control Under Emotion (CCUE) paradigm (from Cohen et al., in press): (a) examples of the fearful, happy, and calm faces used as cues and (b) schematic of one run of the task. In a given run, participants were instructed to respond to one type of cue (go trials) and not to respond to another (no-go trials). These cues were presented within blocks of sustained negative emotion (anticipation of an unpredictable aversive noise), positive emotion (anticipation of an unpredictable monetary reward), and neutral emotion (no event anticipated); the block type was indicated by the background color of the screen (yellow, blue, or purple).

screen (Fig. 1b). (Further descriptions of this task and task-related neural activations are available in other reports: Cohen et al., in press; Dreyfuss et al., 2014; Hare et al., 2008; Somerville et al., 2011). Participants practiced the task prior to entering the scanner, so that they understood the instructions and conditions.

We included both blocks with a sustained state of threat and blocks with a sustained state of excitement in order to dissociate effects of arousal and effects of valence. Threat was induced by telling participants that they might experience an unpredictable aversive auditory stimulus. Excitement was induced by telling participants that they had a chance of winning up to $100. Participants were instructed that the probability of an event occurring, the volume of the noise, and the amount of money won would not be tied to their performance, but rather would be determined by the computer. They were also told that events of a given type would occur randomly, only when the background screen was a particular color (blue for one event and purple for the other). In reality, each participant heard the noise once and won $20 once over the course of the task, and these events occurred in a pseudorandomized order. Each event always occurred near the end of an experimental run, so that these time points could be eliminated from the analyses. During blocks of a sustained neutral state (depicted with a yellow background), participants were told there was no chance of either event occurring as they performed the task. Each state (75-s duration) was induced twice during each run.

Data were acquired in six 8-min 2-s runs (total of 48 min 12 s). Each run consisted of a unique combination of the emotional expressions that served as

go and no-go cues (calm–go/fearful–no go, calm–go/happy–no go, happy–go/fearful–no go, happy–go/calm–no go, fearful–go/calm–no go, fearful–go/happy–no go), in a mixed-block event-related design. Run orders were pseudocounterbalanced, and pairing of the background color and emotional state was counterbalanced. Before each run, participants were told which type of emotional expression was the target and reminded of the meaning of each colored background. We then asked participants a series of four questions to be sure they were aware of each of these contingencies. On each trial, a face appeared for 500 ms; the intertrial interval was jittered (2–7 s). A total of 114 trials were presented in each run, in a pseudorandomized order (84 go trials and 30 no-go trials). For each emotional state, we acquired data on a total of 168 go trials and 60 no-go trials.

Behavioral and psychophysiological data acquisition

Participants completed a final screening for MRI safety before being positioned in the scanner, with a five-button (New York) or four-button (Los Angeles) MR-compatible button box. The experimental task was presented using E-Prime 1.0 (New York) or 2.0 (Los Angeles; Psychology Software Tools, Inc., http://www.pstnet.com) and was projected onto a flat screen mounted in the scanner bore. Participants viewed the screen via a mirror mounted on a 12-channel head coil. Skin conductance response (SCR) was acquired using disposable, isotonic gel electrodes, which were attached to the first and second fingers of the left hand between the first and second phalanges. The electrode cables were grounded through a radio-frequency filter panel. During fMRI scanning, the skin conductance signal was recorded (200-Hz sampling) and amplified using a Biopac recording system and

AcqKnowledge 4.0 software. E-prime software was used to indicate the onset and offset of the emotional states during the task. SCR data were acquired from all the participants.

After exiting the scanner, participants were asked debriefing questions about the believability of task conditions. Specifically, they were asked how much they expected to win money or hear the noise during the blocks in which the background color signaled the possibility of those events (e.g., “Did you expect to win money more during the purple blocks than the blue or yellow blocks?”). Each question was answered using a 7-point Likert scale (1 = *not at all*, 7 = *very much*). Collection of debriefing data from 2 of the 110 subjects was accidently omitted.

fMRI data acquisition

Whole-brain fMRI data were acquired using Siemens Magnetom Trio 3.0-T scanners located at the Citigroup Biomedical Imaging Center at Weill Cornell Medical College or at the Staglin Center for Cognitive Neuroscience at the University of California, Los Angeles. Scanning parameters were identical at the two data-collection sites. A high-resolution, T1-weighted magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) sequence scan was acquired using Biomedical Informatics Research Network (Jovicich et al., 2006) optimized sequences with the following parameters: repetition time (TR) = 2,170 ms, echo time (TE) = 4.33 ms, 256-mm field of view (FOV), 160 sagittal slices with a thickness of 1.2 mm. Functional images were acquired using T2*-sensitive echo planar pulse sequences covering the full brain.

Thirty-eight 4-mm-thick axial slices were acquired per 2,500-ms TR (TE = 30 ms, FOV = 200 mm, flip angle = 90°, 3.1- × 3.1- × 4.0-mm voxels).

Behavioral data analysis

Behavioral data were analyzed for accuracy using the sensitivity index *d′*, which incorporates the rates of both hits and false alarms (Macmillan & Creelman, 2004). We calculated *d′* by subtracting the normalized false alarm rate from normalized accuracy on go trials. Behavioral data, stimulus timing, and emotional-state timing were extracted and calculated using MATLAB and Statistics Toolbox Release 2013b (The MathWorks, Natick, MA). All statistical analyses of the behavioral data were conducted using R (Release 3.1.0; R Core Team, 2014). We tested for age-related differences in performance (*d′*) using analysis of variance (ANOVA) models that included sex and scanning site as between-subjects variables. To investigate performance responding to the emotional cues, without effects of emotional state, we tested for main effects of age group on performance with each cue type in the neutral state. To investigate performance during the emotional states, controlling for effects of the emotional cues, we tested for main effects of age group on performance responding to the calm face cues in each emotional state. A Bonferroni-adjusted alpha of less than .01 was used to correct for multiple comparisons in determining the statistical significance of these ANOVA results. Bonferroni-corrected post hoc *t* tests were used to determine the statistical significance of differences between age groups. Linear and quadratic models were also fitted to each dependent variable, with age modeled continuously. As in the age-group analyses, we used a Bonferroni-adjusted alpha of less than .01 to

determine statistical significance. All analyses were performed on the data from the 110 subjects with usable imaging and behavioral data.

We examined responses to the debriefing questions and the SCR data to assess the efficacy of our emotional-state manipulation. A 1-Hz filter was applied to the raw SCR data. Data were smoothed for each subject. Six subjects had no SCR data because of technical difficulties in the collection of these data, and 29 of the remaining 104 participants had no discernible variation in SCR across the experiment or individual runs and so were removed from the SCR analyses. SCR slope was extracted for each emotional-state block within each run and was *z*-scored within subjects to account for individual differences in SCR. Each individual's average slope was calculated for each emotional state (excitement, threat, and neutral). Change in skin conductance was computed as the difference between average SCR slope in an aroused state (excitement or threat) and average SCR slope in the neutral state. Given the directionality of our hypotheses with respect to these validation measures, we performed one-tailed one-sample Student's *t* tests to test whether responses to debriefing questions were significantly different from 1 (the lowest value on the 7-point scale) and whether SCR differences were significantly different from zero.

fMRI data analysis

Image processing. Functional imaging data were preprocessed and analyzed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). Preprocessing of functional scans included correction for slice-time acquisition using sinc interpolation, volume registration using a 6-parameter rigid-body

transformation to account for head motion, and normalization to the Montreal Neurological Institute (MNI) 152 1-mm T1 template using a 12-parameter affine transformation and nonlinear transformations (AFNI *3dQWarp* function). Data were resampled to 3-mm isotropic voxels and were smoothed using a full-width/ half-maximum Gaussian kernel of 6 mm. Signal intensity of each voxel time series was normalized to percentage signal change.

Image analysis. A general linear model (GLM) was created for each participant to estimate activation in response to the emotional cues and sustained-emotional-state blocks. To disentangle the neural responses to the cues and to the sustained states, which were presented simultaneously, we included 16 regressors in each participant's GLM: 6 task regressors for correct responses to the emotional cues (fearful, happy, or calm faces on go trials and fearful, happy, or calm faces on no-go trials), 3 task regressors modeling the longer (30-TR) sustained emotional states (i.e., the threat, excitement, and neutral sustained states), an additional regressor corresponding to trials with incorrect responses (both go and no-go trials), and 6 motion estimation parameters. Baseline trends were estimated to capture shifts in signal change. Activation in response to the face cues was modeled with a three-parameter gamma hemodynamic-response function (HRF); activation during the sustained states was modeled using a single-parameter block HRF. Time points with motion greater than half a voxel (1.56 mm) were censored, along with the preceding and following time points.

Individual-level regression coefficients for the 110 participants were submitted to group linear mixed-effects (LME) analyses using the AFNI *3dLME* function

(Chen, Saad, Britton, Pine, & Cox, 2013), which is robust to small amounts of missing data. All group-level analyses included a random intercept for each participant and included sex and scanning site as between-subjects variables. Separate models were used to assess effects of transient cues (modeled as brief events) and sustained states (modeled as prolonged blocks) on brain activity. The first group-level LME model assessed effects of the transient cues (fearful, happy, and calm faces) on go and no-go trials. The second group-level LME model assessed effects of the sustained states (threat, excitement, and neutral). Age-group contrasts (general linear tests) were specified within each model to directly probe the neural correlates of behavioral findings. Two additional models assessed effects of the emotional cues and emotional states as a function of exact age as a continuous variable (i.e., interactions of emotional cues or states with exact age).

In group whole-brain analyses, individual voxels were thresholded at a *p* value of .005; the cluster-size threshold was a *p* value of .05 after correction for multiple comparisons (performed using Monte Carlo simulation via the *3dClustSim* program in AFNI). For the threat condition, given our a priori hypotheses regarding differences in prefrontal activation, we used an anatomical region of interest (ROI) for the PFC (obtained from the Harvard-Oxford probabilistic atlas in FSL; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/; Smith et al., 2004). Similar to the PFC ROI in previous studies (e.g., Foerde, Steinglass, Shohamy, & Walsh, 2015), this ROI combined the frontal pole, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus (triangularis and opercularis), frontal medial cortex, subcallosal cortex, paracingulate gyrus, cingulate gyrus anterior division, and frontal orbital cortex bilaterally; a

threshold of 50% probability was used for all subregions within the PFC. A *p* value of .005 was used as the threshold for individual voxels ($p < .05$ after PFC volume correction for multiple comparisons was performed using Monte Carlo simulation via the *3dClustSim* program in AFNI). Regression coefficients for individual participants were extracted from regions with significant effects and were tested for brain-behavior correlations in R (Release 3.1.0; R Core Team, 2014).

Psychophysiological interaction analysis. Generalized psychophysiological interaction (gPPI) analyses (McLaren, Ries, Xu, & Johnson, 2012) were conducted in AFNI to examine task-dependent connectivity across the whole brain. Seed regions were the two PFC regions identified as having age-group effects. The gPPI analyses were carried out by removing sources of noise and artifact, deconvolving the neural signal, extracting the functional time course within the seed regions (5-mm spheres around peak activation), and convolving the time-course data with task timings and the canonical HRF (McLaren et al., 2012). The 16-regressor GLM used for the individual-level image analyses was implemented, but for the gPPI analyses, these models also included regressors for the seed time course and each Time Course $\times$ Task Condition interaction, for a total of 27 regressors. The group-level LME model (controlling for sex and scanning site) was used to test the specific age-group contrasts. Specifically, group-level LME models tested the effects of transient cues (fearful, happy, and calm faces) and sustained states (threat, excitement, and neutral) separately. Age-group contrasts (general linear tests) were specified within each model. The models used a *p* threshold of .05,

corrected for multiple comparisons at the whole-brain level using *3dClustSim*, as described previously.

Results

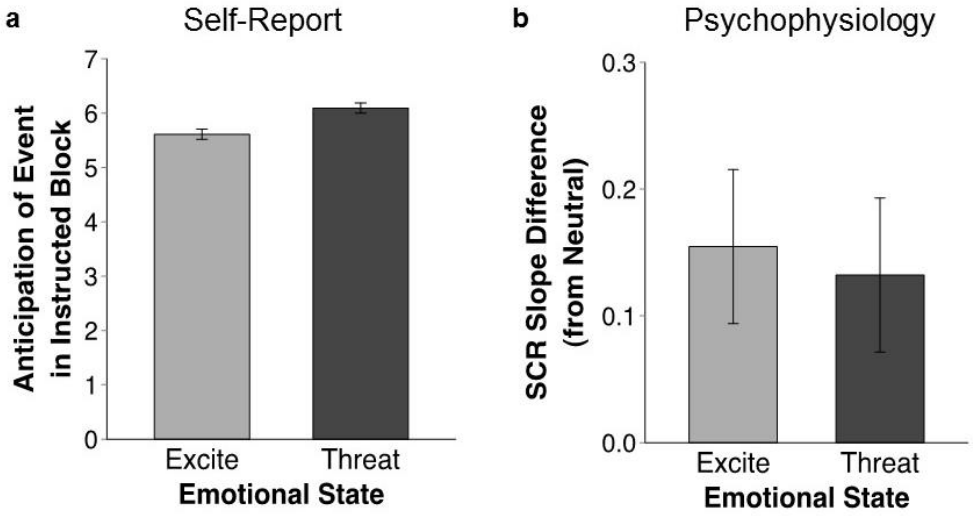

Figure 3.2. Validation of the Cognitive Control Under Emotion (CCUE) paradigm: (a) participants' mean ratings of how likely they thought they were to win money and hear a loud sound in the excitement and threat blocks, respectively, and (b) participants' mean skin conductance response (SCR) during those blocks relative to the neutral blocks. Error bars represent ±1 *SE*.

Behavioral results

Validation of the paradigm. Responses to the debriefing questions and SCR slope differences were tested independently, so we used a Bonferroni-adjusted alpha of less than .025 in our validation tests. These validation measures were collapsed across age. Participants expected both the money, $t(107) = 24.49$, $p < .001$, $d = 3.35$, and loud noise, $t(107) = 31.87$, $p < .001$, $d = 4.36$, to occur during the blocks in which they were led to anticipate these possibilities (Fig. 2a).

Participants' mean SCR difference scores (arousal state minus neutral state) were positive for both the excitement condition, $t(74) = 1.92$, $p = .029$, $d = 0.32$, and the threat condition, $t(74) = 1.65$, $p = .051$, $d = 0.27$ (Fig. 2b). SCR difference scores for the excitement and threat conditions were not significantly different from each other, $t(74) = 0.26$, $p > .250$, $d = 0.04$. These validation results replicate previous results for adults performing this same task (Cohen et al., in press).

Main effects of age for each type of emotional cue. In the neutral-state blocks, there were significant main effects of age group on performance in response to fearful cues, $F(2, 98) = 11.11$, $p < .001$, $\eta_p^2 = .16$; happy cues, $F(2, 98) = 10.90$, $p < .001$, $\eta_p^2 = .15$; and calm cues, $F(2, 98) = 7.81$, $p < .001$, $\eta_p^2 = .10$ (see Fig. 3a and Behavioral Results and Figs. S1a and S2a in the Supplemental Material available online). Post hoc *t* tests revealed that teens and young adults showed diminished performance relative to adults in response to fearful cues—teens versus adults: $t(62.39) = 4.08$, $p < .001$, $d = 0.95$; young adults versus adults: $t(64.82) = 3.33$, $p = .0019$, $d = 0.80$; teens versus young adults: $t(70.09) = 0.61$, $p > .250$, $d = 0.14$. However, young adults and adults showed enhanced performance relative to teens in response to happy cues—teens versus adults: $t(71.15) = 4.14$, $p < .001$, $d = 0.96$; young adults versus adults: $t(65.77) = 1.79$, $p > .250$, $d = 0.43$; teens versus young adults: $t(73.96) = 2.55$, $p = .042$, $d = 0.59$—and only teens and adults differed significantly in their performance with calm cues—teens versus adults: $t(64.05) = 3.54$, $p = .001$, $d = 0.82$; young adults versus adults: $t(64.60) = 1.56$, $p > .250$, $d = 0.38$; teens versus young adults: $t(71.54) = 2.14$, $p = .140$, $d = 0.49$.

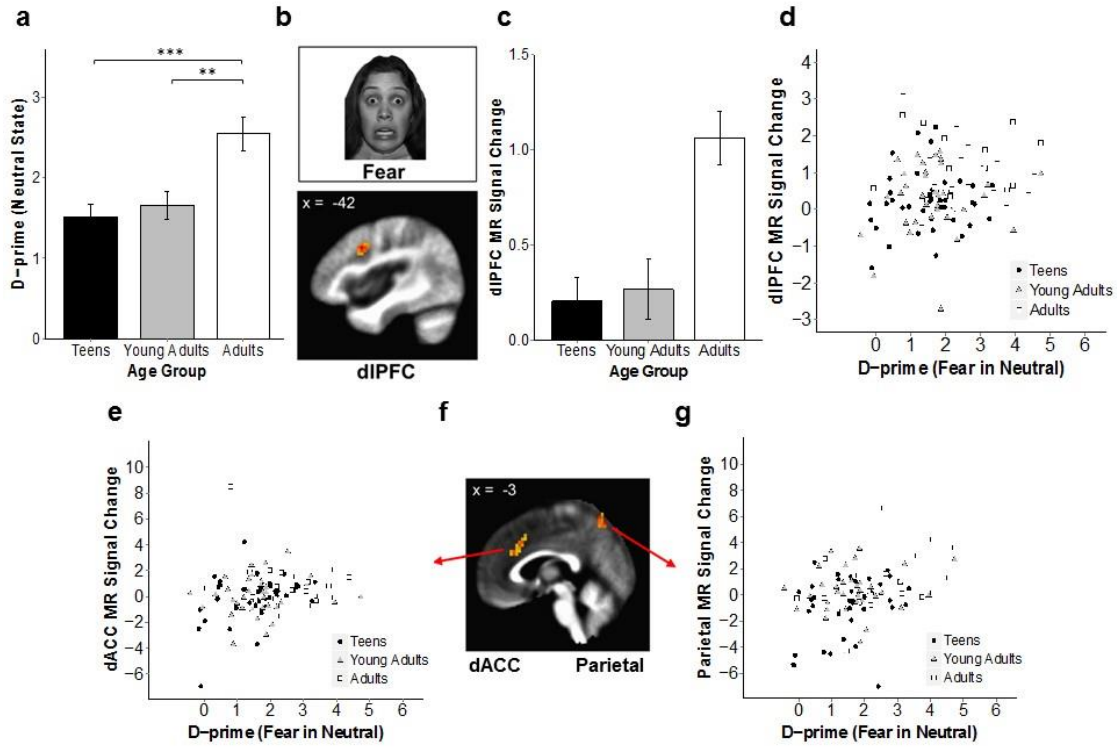

Figure 3.3: Results for the fearful cues. The graph in (a) shows mean performance in response to the brief fearful cues in the neutral-state condition, as indexed by *d′*, for each of the age groups. The brain image in (b) shows the location of the region in the dorsolateral prefrontal cortex (dlPFC) for which signal-change results are presented. The graphs in (c) and (d) show mean signal change in the dlPFC in response to the fearful cues for each age group and as a function of *d′* in the neutral-state condition (separately for each age group), respectively. The brain image in (e) shows the location of the regions in the dorsal anterior cingulate cortex (dACC) and parietal cortex for which mean signal change in response to the fearful cues is graphed as a function of *d′* in the neutral-state condition, separately for each age group, in (f) and (g). Error bars represent ±1 *SE*. Asterisks indicate significant differences (**$p < .01$, ***$p < .001$).

We also examined effects of age as a continuous variable, fitting both linear and quadratic functions to performance with each cue type in the neutral-state blocks. Linear and quadratic functions significantly fit the data for all three cue types—fearful cues, linear: adjusted $R^2 = .12$, $p < .001$, $F(1, 108) = 15.68$; fearful cues, quadratic: adjusted $R^2 = .13$, $p < .001$, $F(2, 107) = 9.23$; happy

cues, linear: adjusted R^2 = .14, p < .001, F(1, 108) = 18.33; happy cues, quadratic: adjusted R^2 = .13, p < .001, F(2, 107) = 9.25; calm cues, linear: adjusted R^2 = .10, p < .001, F(1, 108) = 13.6; calm cues, quadratic: adjusted R^2 = .095, p = .002, F(2, 107) = 6.75. However, the fit of the quadratic function completely overlapped with the fit of the linear function for the calm cues

(see Fig. 4 for performance in response to calm cues in all three sustained emotional states and in response to fearful and happy cues in the neutral-state blocks).

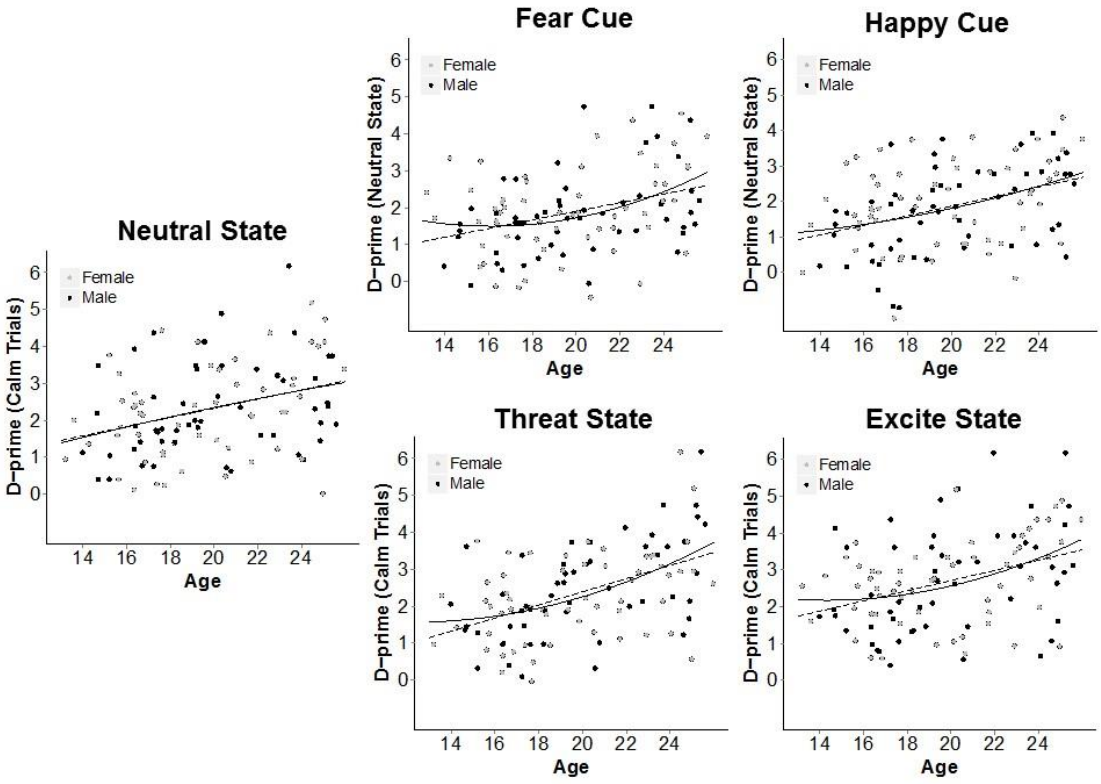

Figure 3.4: Scatterplots showing male and female participants' performance, as indexed by *d′*, as a function of age, along with linear and quadratic functions fitted to the data. Results are shown for each kind of emotional cue in the neutral-state condition, as well as for calm cues in the threat and excitement conditions.

Main effects of age for each emotional state. There were significant main effects of age group on performance in response to calm cues when participants were in emotionally arousing states of threat, $F(2, 98) = 17.57$, $p < .001$, $\eta_p^2 = .24$ (Fig. 5a), and of excitement, $F(2, 98) = 8.65$, $p < .001$, $\eta_p^2 = .13$ (Fig. S1b). Post hoc *t* tests revealed that, although young adults performed better than teens, teens and young adults both showed diminished performance relative to adults under the state of threat—teens versus adults: $t(60.47) = 5.40$, $p < .001$, $d = 1.24$; young adults versus adults: $t(59.51) = 2.75$, $p = .014$, $d = 0.66$; teens versus young adults: $t(73.25) = 3.25$, $p = .014$, $d = 0.64$**.** In contrast, only teens and adults' performance differed significantly under the state of excitement—teens versus adults: $t(58.52) = 4.28$, $p < .001$, $d = 0.98$; young adults versus adults: $t(66.95) = 2.03$, $p = .087$, $d = 0.49$; teens versus young adults: $t(61.39) = 1.83$, $p = .213$, $d = 0.42$.

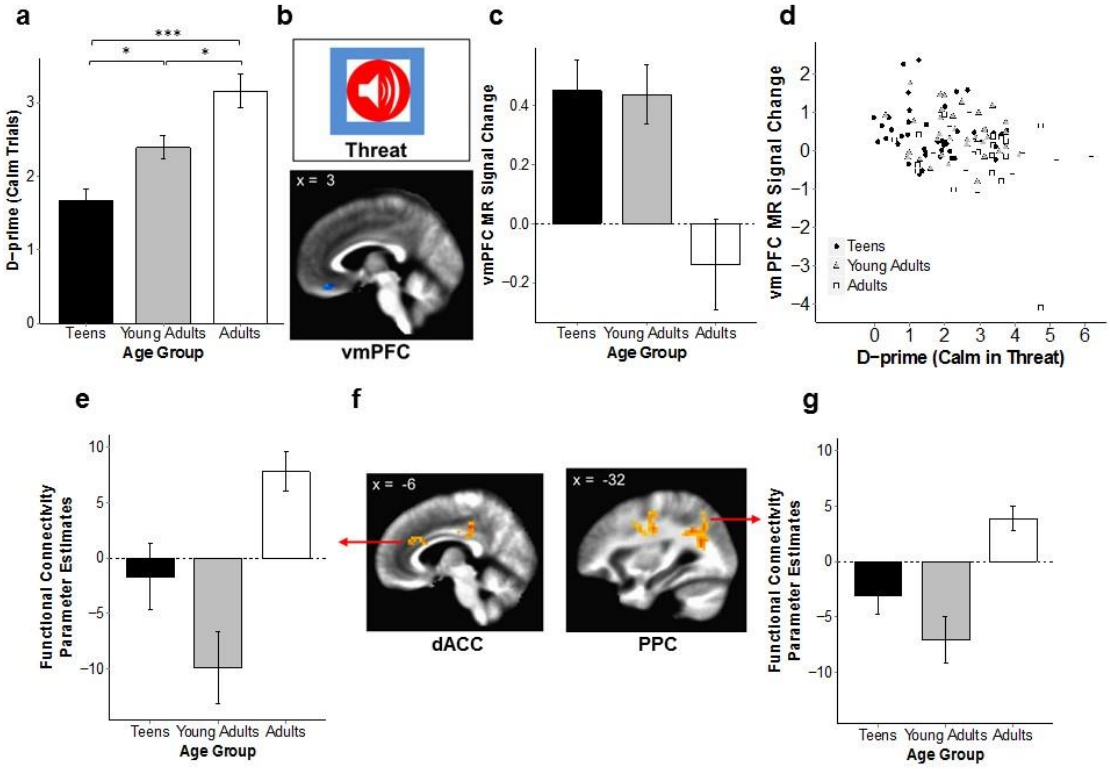

Figure 3.5: Results for the sustained-threat condition. The graph in (a) shows mean performance on calm-cue trials, as indexed by *d′*, for each of the age groups under the sustained state of threat. The brain image in (b) shows the location of the region in ventromedial prefrontal cortex (vmPFC) for which signal-change results are presented. The graphs in (c) and (d) show mean signal change in the vmPFC in the threat condition for each age group and as a function of *d′* on calm-cue trials (separately for each age group), respectively. The brain images show the location of the regions in the dorsal anterior cingulate cortex (dACC) and posterior parietal cortex (PPC) for which functional coupling with the vmPFC is graphed for the three age groups in (e) and (f), respectively. Error bars represent ±1 *SE*. The asterisk indicates a significant difference (**p* < .05, ****p* <.001).

We also examined effects of age as a continuous variable, fitting both linear and quadratic functions to performance in response to the calm cues in each emotional-state condition. We found that both linear and quadratic functions significantly fit the data in both the threat condition—linear function: adjusted R^2 = .23, p < .001, F(1, 108) = 34.08; quadratic function: adjusted R^2 = .24, p < .001, F(2, 107) = 17.78—and the excitement condition—linear function:

adjusted R^2 = .13, p < .001, F(1, 108) = 17.09; quadratic function: adjusted R^2 = .13, p < .001, F(2, 107) = 9.21 (see Fig. 4).

Imaging results

To probe the neural correlates of the observed behavioral effects, we examined blood-oxygen-level-dependent (BOLD) activity in the age-group contrasts specified in the group LME models for each emotional cue and state. Specifically, general linear tests comparing brain activity (relative to implicit baseline, i.e., overall baseline brain activity) of teens and young adults with that of adults were specified for the relevant conditions. We also examined BOLD activity using group LME models in which age was modeled continuously. For these models, in the absence of any specific general linear tests, we examined activation maps showing the interactions of age with type of emotional cue and emotional-state condition.

Effects of emotional cues as a function of age. Two clusters survived whole-brain correction in the age-group analyses of response to fearful cues, showing less activity in teens and young adults than in adults: right dlPFC (x = –41.5, y = –9.5, z = 36.5, 47 voxels; Z = –4.66, p < .02, corrected; Figs. 3b and 3c) and right thalamus (x = –20.5, y = 23.5, z = 6.5, 57 voxels; Z = –3.88, p < .02, corrected). MR signal change in dlPFC was positively correlated with behavioral performance (in the neutral condition) responding to fearful cues across age, r(108) = .203, p = .033 (Fig. 3d), but this correlation did not remain significant when we controlled for age, r(107) = .087, p = .365. A general linear test corresponding to the behavioral result was performed for happy cues in the group-level emotional-cue model to compare brain activity (relative to

implicit baseline) of teens with that of adults and young adults in response to happy cues. A single cluster in the right inferior frontal gyrus (x = –32.5, y = –24.5, z = –11.5, 30 voxels; Z = –4.18, p < .02, corrected) survived whole-brain correction, showing more activity in teens than in both young adults and adults (see Imaging Results Figs. S2b and S2c in the Supplemental Material). No clusters survived whole-brain correction in the analyses of activation in response to calm cues, and no interactions of emotional cue with age group were observed.

Four clusters in the dorsal anterior cingulate cortex (dACC), parietal cortex, and right and left cerebellum survived whole-brain correction when we examined the interaction of age as a continuous variable with type of emotional cue (see Table S1 in the Supplemental Material). In the two largest regions, the dACC and the parietal cortex (Fig. 3e), activity in response to fearful cues was positively correlated with age, $r(108) = .196$, $p = .040$, and $r(108) = .32$, $p < .001$, respectively. MR signal change in response to happy cues was negatively correlated with age in the dACC, $r(108) = -.189$, $p = .048$, but not in the parietal cortex, $r(108) = -.164$, $p = .087$. Activity in response to calm cues was not significantly correlated with age in either of these regions, $r(108) = -.088$, $p = .363$, and $r(108) = -.079$, $p = .412$, respectively.

We examined whether changes in dACC and parietal activity in response to fearful cues were correlated with behavioral performance. In both of these regions, MR signal change in response to fearful cues was positively correlated with d' in the neutral-state condition, $r(108) = .222$, $p = .020$, and $r(108) = .359$, $p < .001$, respectively (Figs. 3f and 3g). Similar patterns were observed even when we controlled for age, $r(107) = .166$, $p = .081$, and $r(107)$

= .277, p = .002. These results suggest that these regions are important for behavioral performance of the task.

Effects of emotional states as a function of age. Although no activations survived whole-brain correction for the contrast of age groups in emotional states, a single cluster in the ventromedial PFC (vmPFC; x = 3.5, y = –33.5, z = –17.5, 13 voxels; Z = 3.58, p < .05, PFC corrected; Fig. 5b) survived PFC volume correction for responses in the state of threat. Teens' and young adults' BOLD activity in the vmPFC during the threat condition showed a sustained increase relative to adults' (Fig. 5c). MR signal change in this region in the threat condition was negatively correlated with behavioral performance (in response to the calm cues) in the threat condition, r(108) = –.308, p = .001 (Fig. 5d), and this correlation remained significant even when we controlled for age, r(107) = –.215, p = .023, and when we removed the one extreme outlier, r(107) = –.253, p = .008. No interactions of emotional state with age group were observed. In analyses for the excitement and neutral-state conditions, no clusters survived whole-brain or PFC volume correction.

A single cluster in the parietal cortex (x = –2.5, y = 68.5, z = 54.5, 29 voxels; F = 11.90, p < .05, corrected) survived whole-brain correction when we examined the interaction of emotional state and age as a continuous variable (see Fig. S3 in the Supplemental Material). MR signal change in this region showed similar positive associations with age in the threat and excitement conditions, r(108) = .181, p = .058, and r(108) = .305, p = .001, respectively, but not in the neutral-state condition, r(108) = .151, p = .116. Because BOLD activity in the threat and excitement conditions showed positive correlations

with age, we collapsed the MR signal across these conditions and tested for associations between activation in this region and behavioral performance (in response to the calm cues) in these conditions. MR signal change was positively correlated with behavioral performance, $r(108) = .209$, $p = .028$ (see Fig. S3), but this correlation did not hold when we controlled for age, $r(107) = .11$, $p = .251$.

Seed-based functional connectivity with prefrontal regions in the three age groups. Whole-brain gPPI analyses were performed using the dlPFC and vmPFC regions as seeds. Nine clusters of voxels showing significantly less functional coupling with the vmPFC in teens and young adults than in adults across the threat condition were observed (see Table S2 in the Supplemental Material). Areas showing this pattern included the dACC (Fig. 5e) and posterior parietal cortex (Fig. 5f). No significant clusters were observed in the age-group contrast for fearful cues using the dlPFC seed.

Discussion

Our findings suggest a developmental shift in cognitive control in negative emotional situations during young adulthood that is paralleled by dynamic developmental changes in prefrontal circuitry. Specifically, young adults showed diminished cognitive control under both brief and prolonged negative emotional arousal relative to slightly older adults, a pattern not observed in neutral or positive situations. This behavioral pattern was paralleled by altered recruitment of lateral and medial prefrontal circuitry in young adults and adolescents, a finding consistent with structural imaging studies showing

protracted development of prefrontal circuitry (Gogtay et al., 2004; Sowell et al., 2004).

Teens' and young adults' diminished cognitive control in response to negative cues was paralleled by their decreased activity in cognitive-control circuitry. When presented with fearful cues, teens and young adults showed less activity than older adults in dlPFC, a region implicated in affective and cognitive regulation (Silvers et al., 2015; Vincent et al., 2008), and in the dACC and parietal cortex. The dlPFC and parietal cortex have reciprocal projections with the dACC, and all three regions have been implicated in cognitive control and are coactivated during cognitive-control tasks (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Platt & Glimcher, 1999; Roy, Shohamy, & Wager, 2012). Further, activity in these regions not only was consistently lower in younger participants, but also was positively correlated with task performance. Together, these findings are consistent with the hypothesis that lower levels of activity within this circuitry in younger individuals reflects diminished cognitive control in the face of negative emotional cues that signal potential threat in the environment.

Although under sustained states of negative emotional arousal (threat) young adults performed better than teens they performed worse than adults. Teens' and young adults' diminished performance relative to adults in the threat condition was paralleled by increased activity in the vmPFC. This region has been implicated in various processes, including self-referential thought and integration of affective information, and is a proposed hub for affective computations and regulation (Roy et al., 2012). Increased sustained

recruitment of the vmPFC under threat in teens and young adults may suggest heightened sensitivity to potential threat, leading to emotional interference and diminished cognitive control. This interpretation is supported in part by our finding of decreased functional coupling of the vmPFC with cognitive-control circuitry of the dACC and posterior parietal cortex in the threat condition among teens and young adults relative to adults. The negative functional connectivity between cognitive and emotional brain regions during this emotional state may underlie the poorer performance of the younger age groups.

Taken together, these findings suggest that young adulthood is a time when cognitive control is still vulnerable to negative emotional influences, in part as a result of continued development of lateral and medial prefrontal circuitry. This temporal developmental shift in cognitive-control capacity in negatively arousing situations relative to neutral (or positive) situations is consistent with the classic notion of developmental cascades in brain and behavior (Casey, Galván, & Somerville, 2015; Masten & Cicchetti, 2010). Accordingly, dynamic brain changes during late adolescence may enhance receptivity to or processing of emotional inputs in order to facilitate meeting changing socioemotional pressures that accompany adulthood (Casey et al., 2015).

Our findings have potential implications for informing age-related legal and social policies. Developmental findings based largely on teens have been referenced in several U.S. Supreme Court decisions regarding treatment of juvenile offenders over the past decade, with the Court acknowledging immature cognitive functioning in juveniles as a mitigating factor in judgments

of criminal culpability (Cohen & Casey, 2014; Scott, 2013; Steinberg, 2013). Scientific research has demonstrated that adolescents show heightened sensitivity to motivational and socioemotional information, which potentially renders them more vulnerable to poor decision making in these situations, compared with younger and older individuals (Chein et al., 2011; Cohen-Gilbert & Thomas, 2013; Dreyfuss et al., 2014; Galvan et al., 2006; Grose-Fifer et al., 2013; Hare et al., 2008; Somerville et al., 2011; Steinberg et al., 2009). The extension of this work to young adults, who show diminished cognitive control relative to slightly older adults in negative emotional situations, may have implications for legal policy. This is not to suggest that teens and young adults should not be held accountable for their actions, but rather, the boundaries of juvenile-court jurisdiction, criminal-court sentencing, and punishment may be informed by developmental considerations (Bonnie & Scott, 2013).

The implications of our findings must be considered within the limitations of the study. First, behaviors were measured within a controlled research setting. Although the emotionally arousing conditions may be relevant to emotional arousal in the real world, they were limited to experimentally manipulated emotional conditions that did not capture the complex real-world situations in which individuals typically make decisions. Second, the sample, although community based and representative of the racial and ethnic distribution in Los Angeles and New York City, was relatively small, with 110 participants 13 to 25 years of age; replication of these findings is warranted.

Prior research examining motivational and social influences on cognitive capacities in young adults as a unique age group has produced mixed results (Chein et al., 2011; Cohen-Gilbert et al., 2014; Silva et al., 2015; Steinberg et al., 2009). The present and previous findings suggest that teens' and young adults' cognitive capacities may be affected differently by various situations. For instance, although negative emotional arousal may diminish cognitive control in both teens and young adults, positive emotional arousal and the presence of peers may not influence young adults as strongly as teens (Chein et al., 2011). Identifying specific situations in which the behavior of young adults may differ from that of slightly older adults will be important in informing potential changes to existing policies and laws. Moreover, further examination of changes in brain structure, activity, and connectivity during this developmental period may provide clearer insights into why and when researchers may or may not observe group-level behavioral changes in young adults.

We examined the influence of emotional arousal on cognitive control from early adolescence through the mid 20s and found that negative emotional arousal, brief or prolonged, affects this capacity in individuals ages 18 to 21 more than in older individuals. Few studies have examined cognitive capacities under emotional influences, and fewer still have taken this approach to study developmental differences in capacities of potential relevance to legal and social policies. Our findings provide support for consideration of contextual influences on behavior and brain function, such as the influence of emotional arousal, when evaluating appropriate age cutoffs for such policies. Although the data in this study do not speak directly to these policy issues,

they may inform dialogues about the age of adulthood in a variety of social and policy contexts.

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Chapter 4:

The impact of emotional cues on memory processes across adolescence

Emotional information can alter actions and choices in the present and thus may also be able to impact subsequent behavior by influencing memory. Adolescence is a time of heightened sensitivity to emotional and social inputs, as dynamic changes in brain structure and function take place. In adults, emotional information has been shown to influence subsequent memory, for better and for worse; however, the impact of emotional and social content on memory across development, as neural circuitries continue to mature, remains unclear. The present study implements an emotional n-back task using happy, fearful, and calm faces as well as places and a surprise memory test to characterize age-related trajectories of recognition memory in individuals ages 9 to 29. Participants were tested for their recognition memory of the stimuli used in the task either immediately after completion or 24 hours later, to allow for memory consolidation. Consistent with previous work, we found that improvements in working memory increased linearly across development. A cubic age pattern best fit immediate recognition memory accuracy, with peak memory for places occurring during adolescence and steady improvements in memory for fearful faces with age. There was no effect of age at 24 hours, however memory accuracy was enhanced for fearful faces relative to other emotions or places across age. These preliminary results suggest that the temporal dynamics of memory for emotional and non-emotional stimuli may be changing across development, which may have implications for behaviors in the short and long-term.

Introduction

Adolescence is often thought of as a rollercoaster ride of emotions and impulsive actions. During this transitional period of development, adolescents navigate many novel experiences and dynamic environments (Spear, 2000; Casey, 2015) alongside widespread structural and functional changes in neural circuitry (Sowell et al., 1999; Gogtay et al., 2004; Raznahan et al., 2014; Simmonds et al., 2014; Mills et al., 2016). A large body of evidence from developmental research has demonstrated that adolescents show a heightened sensitivity to both positive and negative emotional and social information (Galvan et al., 2006; Hare et al., 2008; Steinberg et al., 2009; Chein et al., 2010; Geier et al., 2010; Van Leijenhorst et al., 2010; Somerville et al., 2011; Cohen-Gilbert & Thomas, 2013; Grose-Fifer et al., 2013; Dreyfuss et al., 2014) that often motivates them towards action (Casey, 2015). Given the observed increased reactivity towards socioemotional information during this stage of development, how might emotions influence memory for specific events?

Emotions have been shown to influence episodic memory, for better and for worse, in adults (Gagnon & Wagner, 2016; Kensinger, 2004; LaBar & Cabeza, 2006; McGaugh, 2004; Phelps, 2006; Yonelinas & Ritchey, 2015). Emotional stimuli, particularly negative stimuli such as negative scenes, stories, and words or neutral stimuli paired with an aversive stimulus such as a loud noise or a shock, are better remembered than neutral stimuli (Hamann, 2001; LaBar & Cabeza, 2006; McGaugh, 2004; Phelps, 2006). These effects typically emerge after a delay of several hours and are often smaller or sometimes

absent when memory is tested immediately (Andersen et al., 2006; Sharot & Phelps, 2004; Sharot & Yonelinas, 2008; Sharot et al., 2007). The emotional memory enhancement effect appears to be specific to the emotional item or object (Kensinger, 2007; Mather, 2007), as contextual details surrounding an emotional event do not show a recollection boost (Sharot & Yonelinas, 2008; Mather & Knight, 2008; Kensinger & Schacter, 2006). In contrast, flashbulb memories and the accompanying surrounding events are rapidly forgotten and inconsistently remembered in the long-term, although confidence in memory remains high (Hirst et al., 2009; 2015; Hirst & Phelps, 2016). Stress also often impairs retrieval of both emotional and neutral information (Domes et al., 2004; Kuhlmann et al., 2005; Schwabe et al., 2012) and, similarly to emotional memory enhancement effects, these effects also seem to emerge over time (Schwabe & Wolf, 2014). Thus, the nature of the effects of emotion on memory—i.e. whether memory is enhanced, unaffected, or diminished—varies depending on the type of emotion, the form of recollection that is assessed, and the amount of time that has elapsed between the event and when memory is assessed.

Early evidence of developmental changes in memory processes come from the studies of “infantile amnesia,” or the inability to retrieve episodic memories from early in development. This phenomenon has been observed across species and specifically influences memories from before the ages of approximately two to four years in humans (Rubin, 2000; Hayne & Jack, 2011; Li et al., 2014). There is also evidence of adolescent specific differences in memory. Research in humans shows evidence of a reminiscence bump, such that people tend to show better recollection for autobiographical memories

(Rubin et al.,1998) and popular culture-related memories (Janssen et al., 2012) from adolescence and young adulthood, relative to other periods of life. Studies of fear learning and extinction, primarily carried out in rodents, also reveal adolescent specific memory effects, showing persistent fear memories in adolescents relative to younger and older ages (Kim et al., 2011; Pattwell et al., 2012; Baker et al., 2016). Still, few studies have examined emotional episodic memory across development in humans and fewer still have focused on adolescence.

Multiple memory systems, centered on the amygdala for emotional memory and the hippocampus for episodic and declarative memory, are proposed to interact for memory of emotional events (McDonald et al., 2004; Phelps, 2004). An emotional binding account of episodic memory proposes that the amygdala binds emotional information to an item, communicating with both the perirhinal cortex and hippocampus, to modulate encoding, storage, and recollection of these memories (Yonelinas & Ritchey, 2015). In humans, the amygdala and hippocampus show different, dynamic trajectories of structural development. The amygdala shows a quadratic volumetric trajectory, with peak volume around age 16 (Mills et al., 2014), whereas the hippocampus shows volumetric increases until around ages 13-14 followed by a protracted course of volumetric decreases and increases in anterior and posterior hippocampus throughout adolescence and into adulthood (Daugherty et al., 2016; Lee et al., 2014; Gogtay et al., 2006; Tamnes et al., 2014). Furthermore, both the prefrontal and parietal cortices implicated in working memory processes also show protracted development in young adulthood (Gogtay et al., 2004; Simmonds et al., 2014; Mills et al., 2016). Differences in both

hippocampal and prefrontal activity and connectivity in working memory tasks are evident throughout adolescence (Finn et al., 2010). Together, these studies showing that the neural circuitry underlying emotional episodic memory processes continues to develop into adulthood and research showing developmental sensitivities to emotional inputs suggest the potential for developmental differences in recognition memory for emotional items.

Two divergent hypotheses arise from the observations of heightened sensitivity to emotional information during adolescence. Emotional events are particularly salient to adolescents, so we might hypothesize that they will have better memory for these events; however, considering the multitude of socioemotional experiences adolescents encounter on a daily basis, we might hypothesize that if everything is salient, the events may start to blur together or compete. There is evidence to suggest that emotional information, both emotional faces and non-face pictures, enhances memory in adolescents (Nelson et al., 2003; Vasa et al., 2011; Pinabiaux et al., 2013) and that recall for emotional pictures is comparable to that of adults (Nelson et al., 2003; Vasa et al., 2011). These extant studies have only examined recognition memory within an hour of the encoding task, binned by age groups, and only included child and adolescent participants (Pinabiaux et al., 2013) or adolescent and adult participants (Nelson et al., 2003; Vasa et al., 2011).

The current study examined recognition memory for stimuli presented in an emotional n-back working memory task in individuals ages 9 to 29, spanning the transition into and out of adolescence. This working memory task consists of blocks with emotional (happy and fearful faces) and neutral (calm faces and

places) stimuli. Incorporating both neutral faces and places allows for a control that incorporates social information and a control without any social or emotional information, respectively. We administered a surprise recognition memory test to two groups of participants, one receiving the test immediately after completing the emotional n-back task and the other 24 hours later. We examined age continuously in order to determine distinct patterns of age-related change by cue type. We hypothesized that adolescents would show similar recognition memory to adults in the immediate condition and that adolescent specific differences in memory for emotional cues would emerge after 24 hours.

Methods

Participants

One hundred and thirty-three participants, ages 9 to 29 years, were recruited to participate in the study. Thirty-three participants were excluded for poor performance on the working memory task (< 75% accuracy in the 0-back condition, on which subjects should be near ceiling due to low memory load). Three additional subjects were excluded for not returning for their second appointment. Behavioral data from 97 subjects (46 males and 51 females; mean age = 18.49; SD = 5.92) are reported in the final analyses (Figure 4.1). Subjects were randomly assigned to an immediate recall condition (n = 49; 22 males and 27 females; mean age = 18.10; SD = 5.95) or a 24-hour recall condition (n = 48; 24 males and 24 females; mean age = 19.62; SD = 5.85). Participants were recruited from a diverse community sample in the New York City area and self identified as Caucasian (41.2%), African American (20.6%),

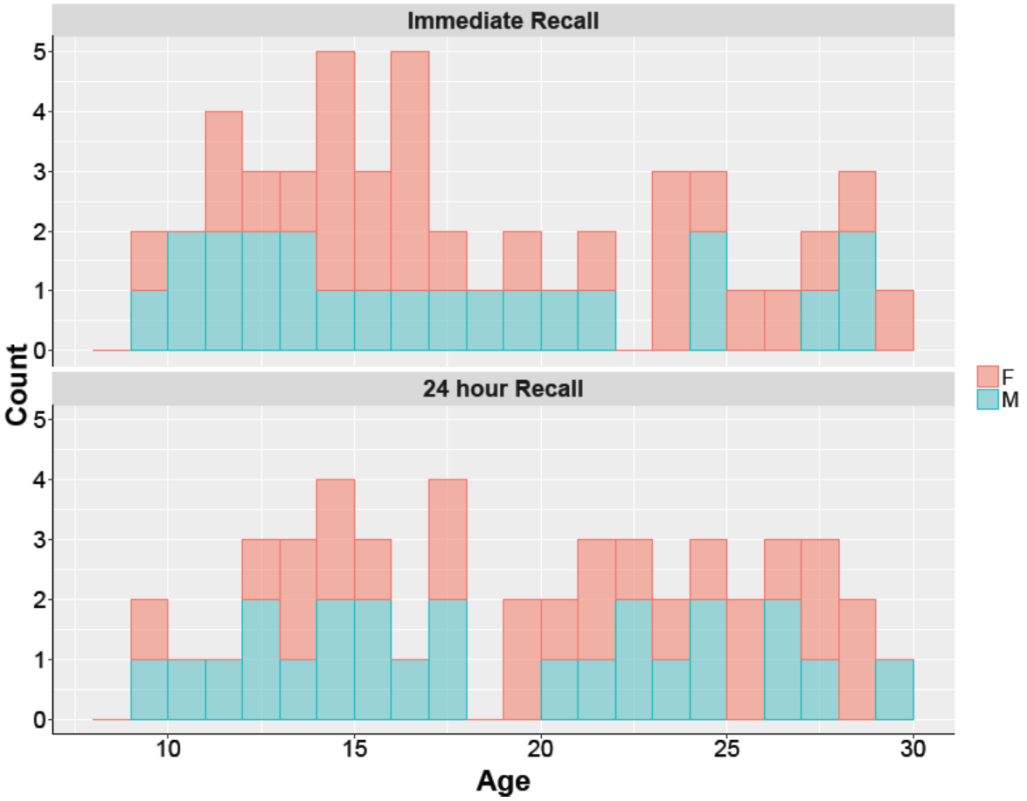


Figure 4.1: Histogram representing age and sex distribution of participants.

Asian (10.3%), Hispanic (20.6%), and Other (6.2%). Participants reported no use of psychotropic medications or past diagnoses of, or treatment for, psychiatric or neurological disorders. All participants provided informed written consent and minors provided written assent approved by the Institutional Review Board at Weill Cornell Medical College.

Emotional n-back behavioral paradigm

The N-back task used in the present study (Figure 4.2) was modified from the Human Connectome Project N-back task (http://www.humanconnectome.org/; Barch et al., 2013). The N-back task had two runs consisting of eight blocks each. Each block consisted of 10 trials (2.5 s each) and 4 fixation blocks (15 s each). Each trial consisted of a stimulus presented for 2 s, followed

immediately by a 500 ms fixation cross. Of the 10 trials in each block, 2 were targets, 2–3 were non-target lures (e.g., repeated stimuli in the wrong n-back position, either 1-back or 3-back), and the remainder were non-lures (i.e., stimuli only presented once). There were a total of 160 trials using 96 unique stimuli.

Four different stimulus types (24 unique stimuli of each type) were presented in separate blocks in each run. On each trial, the participants were asked to rate the picture as a “Match” or “No Match.” Participants were told to make a response on every trial. In each run, four blocks were a 2-back working memory task—participants were instructed to respond “match” when the current stimulus was the same as the one shown two back— and four blocks were a 0-back working memory task—participants were instructed to respond “match” when the current stimulus was the same as the target presented at the start of the block. At the start of each block, a 2.5 s cue indicated the task type (“2-back” or “target =” and a photo of the target stimulus). In this emotional variant of the task, blocks of trials consisted of happy, fearful, and neutral facial expressions as well as places. The facial stimuli were obtained from the Racially Diverse Affective Expressions (RADIATE) set of stimuli (Conley et al., in prep) and places stimuli were obtained from previous studies (Kanwisher, 2001; O’Craven and Kanwisher, 2000; Park and Chun, 2009).

Prior to completing the task, participants all completed a brief training and practice. The training described the 0-back and 2-back memory tasks and walked through step by step examples of how the participant should respond in each block, with feedback. This was immediately followed by a brief

simulation of the task consisting of four blocks (2 of each n-back memory task; 2 face blocks, 2 place blocks) consisting four trials each. The stimuli used in the practice were different from those in the task.

Recognition memory test procedures

The surprise recognition memory test (Figure 4.2) included 96 old stimuli presented during the emotional n-back task and 96 new stimuli, with equal numbers of each stimulus type in the old and new stimulus sets (24 each of happy, fearful, and neutral facial expressions as well as places in each set). A total of 192 pictures were presented during the recognition memory test. Participants were asked to rate each picture as either “Old” or “New.” Each

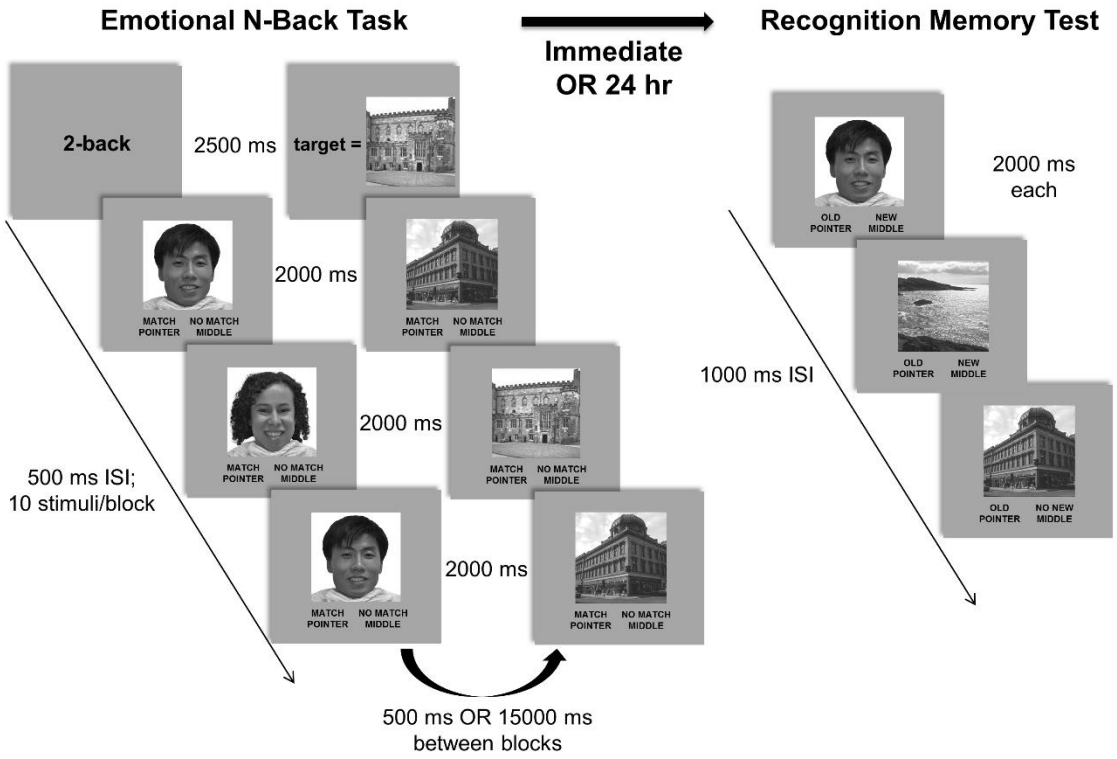


Figure 4.2: Experimental paradigm. Schematic of 2-back (happy face) and 0-back (place) blocks of the emotional n-back task and examples of trials in the subsequent memory test.

picture was presented for 2 s followed immediately by a 1s presentation of a fixation cross. Instructions and a 2-trial practice (one “Old” from the task practice and one new stimulus) preceded the memory test. Participants were randomly assigned to an immediate recall condition or a 24-hour recall condition.

Explicit knowledge regarding the memory test

Prior to administering the recognition memory test (either immediately after the emotional n-back or 24 hours later), we assessed whether participants expected the surprise memory test via two questions described in a previous study of recognition memory (Dunsmoor et al., 2015). We first asked participants “Do you have any expectations of what this next task in the experiment will be: yes or no?” Once participants had answered this question, they were told that the next experiment would test their memory for the pictures presented in the earlier game. Participants were then asked to indicate “How surprised are you that there is a memory test?” on a 5-point scale from 1 “I did not expect a memory test at all” to 5 “Yes, I knew there would be a memory test.” Participants who responded “Yes” to the first question and “5” to the second questions were to be excluded from analyses, however none of the participants in the present sample met both criteria.

Behavioral data analysis

Trial by trial accuracy data from the emotional n-back and recognition memory test were extracted using MATLAB R2016a and analyses were conducted using R version 3.3.2 (R Core Team, 2016). General linear mixed effects models using the lme4 package (Bates et al., 2014) were used to perform

binomial logistic regressions with random effects for participants. To determine patterns of age-related change, linear, quadratic, and cubic patterns were tested by incorporating polynomial terms of mean-centered age (using the poly function to compute orthogonal polynomials) and their interaction with the fixed effect of stimulus type (neutral, place, happy, fear) into the model. This allowed for assessment of differences in age-related patterns of behavioral change in response to fearful, happy, and place stimuli relative to neutral face stimuli. Neutral face stimuli were used as the baseline, as these stimuli allowed for control of the social information inherent to face stimuli. These nested models were tested for goodness of fit as compared to a model including only the fixed effect of stimulus type (no age terms) using a χ^2 test.

Following the identification of the best fitting age model, covariates were then each added individually to the model and compared directly to the simpler model using a χ^2 test. A p-value < 0.05 on the χ^2 test was taken to indicate that the covariate explained a significant amount of variance; otherwise the simpler model was preferred. For models assessing emotional n-back task performance, fixed effects of sex and recognition memory condition (0 hr or 24 hr) were each tested; for models assessing recognition memory for old stimuli, fixed effects of sex, working memory accuracy, and back condition (0-back or 2-back) were each tested; and for models assessing recognition memory for new stimuli, only fixed effects of sex were tested. Full descriptions of the best fitting models are reported.

Results

Emotional n-back task

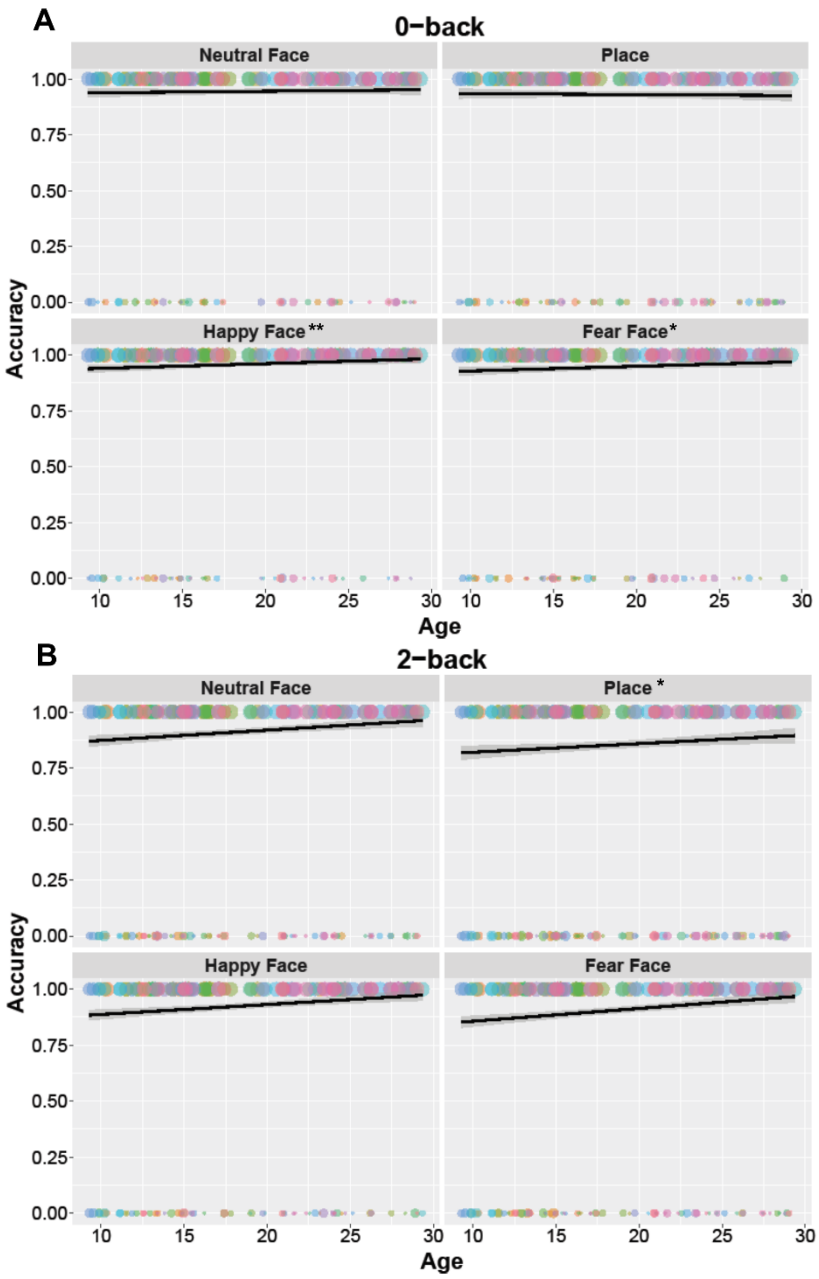


Figure 4.3: Emotional n-back task performance. A) Accuracy in the 0-back task increases linearly with age in response to happy and fearful faces. B) Accuracy in the 2-back task increases linearly with age across stimulus type, with diminished accuracy across age for places. Each colored dot represents a participant and is scaled based on number of trials. Lines of best fit shown with 95% confidence interval. * = $p < 0.05$, **= $p < 0.01$

We tested for age effects in performance of the 0-back and 2-back components of the task separately. The relationship between mean-centered age and working memory task accuracy was best described by the linear age model for both the 0-back ($\chi^2(4) = 11.05$, $p = 0.026$; Figure 4.3A) and 2-back ($\chi^2(4) = 19.15$, $p < 0.001$; Figure 4.3B) components of the task. Model fits were not improved by the inclusion recognition memory condition (0-back model, $\chi^2(1) = 0.01$, $p > 0.250$; 2-back model, $\chi^2(1) = 0.12$, $p > 0.250$) or sex (0-back model, $\chi^2(1) = 0.25$, $p > 0.250$; 2-back model, $\chi^2(1) = 0.29$, $p = 0.09$) as fixed effects, thus the simpler models were preferred. The 0-back model showed significant improvements in working memory accuracy with age in response to happy faces ($\beta = 23.14$, $p = 0.008$) and fearful faces ($\beta = 15.78$, $p = 0.049$) relative to neutral faces (see Table 1 for full descriptions of the model). The 2-back model showed significantly diminished working memory accuracy across age in response to places ($\beta = -13.66$, $p = 0.03$) relative to neutral faces and a main effect of accuracy increasing with age ($\beta = 28.39$, $p < 0.001$), but no significant differences in performance with age in the emotional conditions relative to neutral (see Table 1 for full descriptions of the model).

Table 4.1. Best fitting working memory models

	Variance	SD	*β*	SE	z value	*p*
0-back						
Random effect						
Intercept	0.59	0.77				
Fixed effect						
Intercept			3.09	0.13	23.46	< 0.001
Place			-0.25	0.13	-1.88	0.060

Happy Face			0.39	0.15	2.53	0.011
Fear Face			0.09	0.14	0.63	> 0.250
Age[1]			9.21	7.67	1.20	0.230
Place * Age[1]			-10.47	8.72	-1.20	0.230
Happy Face * Age[1]			23.14	8.77	2.64	0.008
Fear Face * Age[1]			15.78	8.02	1.97	0.049
2-back						
Random effect						
Intercept	0.38	0.62				
Fixed effect						
Intercept			2.55	0.11	24.04	< 0.001
Place			-0.64	0.11	-6.11	< 0.001
Happy Face			0.19	0.12	1.60	0.111
Fear Face			-0.61	0.12	-0.52	> 0.250
Age[1]			28.39	6.35	4.47	< 0.001
Place * Age[1]			-13.66	6.29	-2.17	0.030
Happy Face * Age[1]			3.74	6.83	0.55	0.584
Fear Face * Age[1]			5.58	7.42	0.75	0.452

Linear age term is represented by Age[1]

Recognition memory test

We tested for age effects in recognition memory for old (stimuli presented in the emotional n-back task) and new stimuli in the immediate recall and 24 hour recall groups separately, by old or new stimuli and by recall group. Recognition memory accuracy for old stimuli was best described by the cubic model for the immediate recall group ($\chi^2(4) = 17.71$, $p = 0.001$; Figure 4.4A)

and by the simplest model containing only the fixed effect of stimulus type and

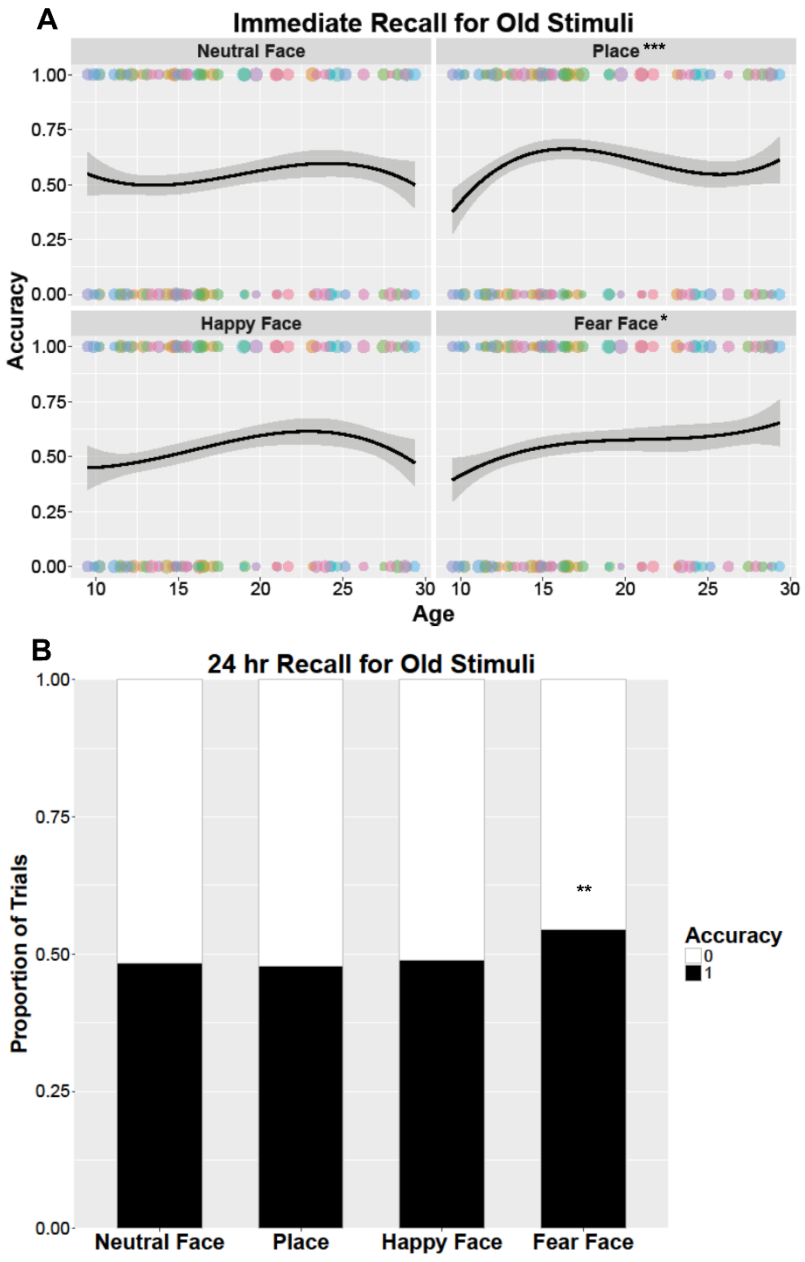


Figure 4.4: Recognition memory for stimuli presented in the emotional n-back. A) Immediate recall accuracy for old stimuli shows cubic age-related patterns of change. Each colored dot represents a participant and is scaled based on number of trials. Lines of best fit shown with 95% confidence interval. B) 24 hour recall accuracy for old stimuli shows no effect of age, but is enhanced for fear faces across age. * = $p < 0.05$, **= $p < 0.01$, ***= $p < 0.001$

no age for the 24 hour recall group (Figure 4.4B). Model fits were not improved by the inclusion trial by trial emotional n-back performance (immediate group model, $\chi^2(1) = 0.92$, $p > 0.250$; 24 hour group model, $\chi^2(1) = 1.61$, $p = 0.204$) or sex (immediate group model, $\chi^2(1) = 0.480$, $p > 0.250$; 24 hour group model, $\chi^2(1) = 0.07$, $p > 0.250$) as fixed effects. While model fit was not improved by the inclusion of back condition in the 24 hour group model ($\chi^2(1) = 0.07$, $p > 0.250$), this parameter significantly improved model fit in the immediate group model ($\chi^2(1) = 9.69$, $p = 0.002$) and was therefore retained as a covariate. The cubic model for the immediate recall group showed a main effect of back condition ($\beta = -0.19$, $p = 0.002$), such that memory for stimuli in the 2-back task was worse than memory for stimuli in the 0-back task. The immediate recall group also showed significant effects of cubic mean-centered age on recognition memory accuracy for places ($\beta = 21.62$, $p < 0.001$) and fearful faces ($\beta = 12.85$, $p = 0.012$) relative to neutral faces, such that place memory increased into mid-adolescence and subsequently decreased in the mid-twenties whereas fearful face memory showed gradual non-linear increases with age (see Table 2 for full descriptions of the model). The no age model for the 24 hour recall group showed improved recognition memory for fearful faces ($\beta = 0.27$, $p = 0.002$) relative to neutral faces (see Table 2 for full descriptions of the model).

Table 4.2. Best fitting recognition memory for old stimuli models

	Variance	SD	*β*	SE	z value	*p*
Immediate recall						
Random effect						
Intercept	0.21	0.46				

Fixed effect						
Intercept			0.23	0.09	2.51	0.012
Place			0.24	0.09	2.80	0.005
Happy Face			-0.02	0.09	-0.17	> 0.250
Fear Face			0.06	0.09	0.71	> 0.250
Age^1			5.90	5.02	1.18	0.239
Age^2			-2.16	5.09	-0.43	> 0.250
Age^3			-7.98	5.16	-1.55	0.122
2-back			-0.19	0.06	-3.11	0.002
Place * Age^1			-2.97	4.92	-0.60	> 0.250
Happy Face * Age^1			3.72	4.84	0.77	> 0.250
Fear Face * Age^1			9.93	4.85	2.05	0.041
Place * Age^2			-12.11	5.14	-2.36	0.019
Happy Face * Age^2			-8.72	4.87	-1.79	0.073
Fear Face * Age^2			-2.86	5.05	-0.57	> 0.250
Place * Age^3			21.62	5.19	4.17	< 0.001
Happy Face * Age^3			1.72	4.92	0.35	> 0.250
Fear Face * Age^3			12.85	5.11	2.52	0.012
24 hr recall						
Random effect						
Intercept	0.37	0.61				
Fixed effect						
Intercept			-0.07	0.11	-0.64	> 0.250
Place			-0.02	0.09	-0.27	> 0.250
Happy Face			0.02	0.09	0.26	> 0.250
Fear Face			0.27	0.09	3.08	0.002

Linear age term is represented by Age[1], quadratic term by Age[2], and cubic term by Age[3]

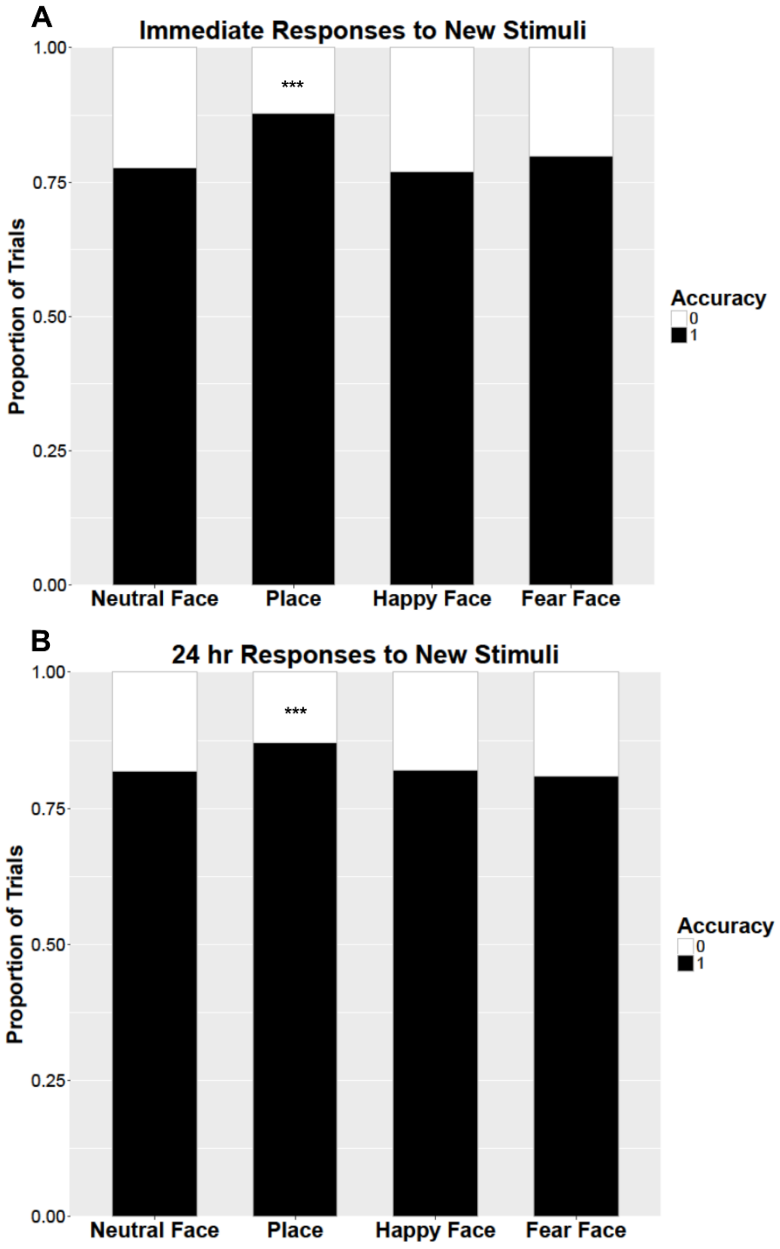


Figure 4.5: Recognition memory test responses to new stimuli. A) Immediate accuracy for identifying new stimuli as new is increased for places across age. B) 24 hour accuracy for identifying new stimuli as new is increased for places across age. ***= $p < 0.001$

Recognition memory accuracy for new stimuli was best described by the simplest models containing only the fixed effect of stimulus type and no age for both the immediate (Figure 4.5A) and the 24 hr (Figure 4.5B) recall groups. Model fits were not improved by the inclusion of sex as a fixed effect (immediate group model, $\chi^2(1) = 0.10$, $p > 0.250$; 24 hour group model, $\chi^2(1) = 0.22$, $p > 0.250$). The model for the immediate recall group showed better accuracy at correctly identifying a new stimulus as new for places relative to neutral faces in both the immediate ($\beta = 0.12$, $p < 0.001$) and 24 hour ($\beta = 0.14$, $p < 0.001$) recall groups (see Table 3 for full descriptions of the models).

Table 4.3. Best fitting recognition memory for new stimuli models

	Variance	SD	β	SE	z value	p
Immediate recall						
Random effect						
Intercept	0.59	0.77				
Fixed effect						
Intercept			1.39	0.13	10.54	< 0.001
Place			0.78	0.12	6.79	< 0.001
Happy Face			-0.42	0.10	-0.41	> 0.250
Fear Face			0.14	0.10	1.37	0.171
24 hr recall						
Random effect						
Intercept	0.67	0.82				
Fixed effect						
Intercept			1.71	0.14	11.85	< 0.001
Place			0.45	0.12	3.74	< 0.001

Happy Face	0.01	0.11	0.11	> 0.250
Fear Face	-0.69	0.11	-0.62	> 0.250

Discussion

The preliminary findings of this study suggest that distinct patterns of age-related differences in memory for emotional and non-emotional stimuli emerge when memory is assessed in the moment (working memory), immediately after encoding (short term memory), and after consolidation (long term memory). Working memory accuracy increased linearly across development, with more substantial gains in accuracy for emotional stimuli under low memory load and better accuracy across age for faces than places under higher load. Subsequent memory assessed immediately after encoding showed a cubic relationship with age, such that memory for places peaked in adolescence whereas memory for fearful faces showed pronounced gains from childhood to mid-adolescence and steady improvement into adulthood. Finally, recognition memory assessed after 24 hours showed no effect of age, but did show better memory for fearful faces across age, consistent with previous work showing enhanced memory for negative emotional stimuli in both adults and adolescents (Hamann, 2001; Nelson et al., 2003; LaBar & Cabeza, 2006; McGaugh, 2004; Kensinger & Schacter, 2006; Phelps, 2006; Vasa et al., 2011; Keightley et al., 2011; Pinabiaux et al., 2013).

Although age-related differences in working memory were not the primary focus of the present study, age-related effects on working memory were observed in the emotional n-back task. The ability to hold information in mind

and to use this information in goal directed responses is believed to be functional by middle childhood (Bunge & Wright, 2007). Consistent with findings that children are able to retain information in mind, comparable performance across age in response to neutral faces and places in 0-back condition in the present study. However, modest yet significant linear gains in performance were observed from childhood to adulthood in response to both happy and fearful faces in this low memory load condition. This what (pattern? Observation?suggests that emotional information may impact the ability to hold information in mind in children and teens relative to adults. In the higher working memory load 2-back condition, linear increases in performance with age were observed across cue types, consistent with normative data on n-back task performance showing age related increases in performance for 1-, 2-, and 3-back working memory loads (Pelegrina et al., 2015). Despite similar linear patterns across cue types, performance was diminished for places across age. Still, these findings of age-related differences in two different memory loads generally point to linear increases in performance across age.

A cubic relationship between age and recognition memory emerged when memory was tested immediately after encoding. Memory for both neutral and happy faces showed similar age-related patterns, with gradual increases in memory accuracy into the early twenties. In contrast, recognition memory for places showed steep improvement into mid-adolescence, followed by declines in the mid-twenties. The enhancement of memory for places throughout adolescence that later diminishes in adulthood may have several possible explanations. It is possible that the increased number of faces—all of which are social cues, which may be particularly salient to adolescents (Chein et al.,

2010; Steinberg et al., 2009; Somerville et al 2011; Jones et al., 2014)— in this task relative to places creates interference, which results in adolescents showing better memory for unique places. Alternatively, there is evidence to suggest that face specialization and improvements in face recognition increase with age, as responses to non-face stimuli diminish (Gomez et al., 2017; Zhu et al., 2016). These studies show differential structural (Gomez et al., 2017) and functional (Zhu et al., 2016) development of brain areas associated with face processing and social cognition, including the fusiform gyrus, superior temporal sulcus, and inferior orbital cortex. Previous studies have shown that different areas of functionally defined face (fusiform face area, superior temporal sulcus) and place (parahippocampal place area) selective cortex show different patterns of structural volume in children, teens, and adults (Golarai et al., 2007) and that face selective regions continue to develop into adolescence (Grill-Spector et al., 2008). Thus, the boost in place memory observed during adolescence may be attributable to imbalances in the maturation of place and face selective areas of cortex and their interactions with neural circuitry implicated in memory processes across development.

Relative to neutral faces, immediate recognition memory for fearful faces initially improved more rapidly with age, into the mid to late teens, and then showed gradual improvement from late adolescence to adulthood. This result suggests that subsequent memory for fearful faces, or cues that indicate a potential threat in the environment, shows an accelerated trajectory of improvement in recall relative neutral or positive faces. While fearful faces still appeared to be prioritized in memory after 24 hours, there were no observed

age effects in recognition memory. Across ages, we found that memory for fearful faces was enhanced relative to neutral faces after 24 hours and that there were no significant differences in memory for happy faces or places relative to neutral faces. This temporal dissociation in age-related patterns of memory for fearful stimuli may suggest that a period of consolidation allows for memory of these salient cues to become comparable to that of adults. Previous work has shown that a period of sleep allows children to convert implicit knowledge into explicit knowledge and to show even better explicit recall of learned sequences relative to adults (Wilhelm et al., 2013). Thus, allowing for consolidation may serve to ameliorate age-related differences in recognition memory.

No age-related effects were observed in responses to new stimuli presented during the recognition memory test in either the immediate recall or 24 hour recall group. Both groups of participants showed a similar pattern of performance whereby, across ages, participants were more accurate in identifying new places as new relative to neutral faces. There were no differences in accuracy for emotional facial expressions relative to neutral faces. While the comparable, relatively lower levels of accuracy for identifying new faces as new may suggest a general familiarity bias for faces, a tendency to rate new faces as old, relative to places, this potential bias is similar across face type and no age-related differences were observed. Thus, the lack of face type or age effects indicates that the age-related differences observed in the immediate recall condition and enhanced memory for fearful faces in the 24 hour recall condition were not driven by a generally increased propensity for participants to rate stimuli as previously seen (old).

Taken together, these results suggest differing age-related patterns of working, short term, and long term memory for emotional and non-emotional stimuli may point to a shift in the temporal dynamics of memory processes. A shift in age-related patterns of memory processes over time may be due to the asymmetric developmental trajectories of face and place selective cortices (Golarai et al., 2007; Grill-Spector et al., 2008; Gomez et al., 2017) as well as connectivity with neural systems that support emotional episodic memory processes, such as the hippocampus, amygdala, and prefrontal cortex (Gogtay et al., 2004; Simmonds et al., 2014; Mills et al., 2014; Yonelinas & Ritchey, 2015; Daugherty et al., 2016). These findings may have implications for better understanding the unique patterns of behaviors often observed throughout adolescence (Steinberg, 2005; Ernst et al 2006; Casey et al., 2008; Blakemore & Robbins, 2012; Casey, 2015), as the relationship between age and memory process changes both as function of cue type and time elapsed since encountering the cue. The present study also finds that memory for fearful faces—cues the are indicative of a potential threat in the environment—shows relatively accelerated improvement in the short term with age. Memory for cues of potential threat is enhanced after memory consolidation across all age, suggesting a potential prioritization in memory of cues that may signal threat and may be relevant for the survival of the organism.

The reported findings must be considered in light of limitations. With a total of 97 subjects across two experimental groups, the present study has a small sample size to asses developmental effects. Replication of these findings is

warranted and data collection of a second sample is under way. The small sample size in the present study is primarily due to participants excluded for poor task performance, which seemed largely attributable to confusion about which task (0-back or 2-back) the participant was playing in any given block. We have modified the task presently being run to include a 500 ms colored fixation that precedes each task type slide, to draw the participant's attention to the task prompt. The increased number of faces relative to places also makes it difficult to ascertain whether observed differences in memory and responses to place stimuli may be due to the relative infrequency of these stimuli in the tasks versus being attributable to non-emotional and non-social stimuli per se. Additional studies with equal amounts of different stimulus types would clarify these effects. Finally, although we used neutral faces as the baseline to control for social information inherent in faces, it is possible that different patterns of results may be observed for emotional non-face stimuli, due to the confound of older participants having more experience with faces. Further similarly structured studies that include emotional scenes or neutral cues paired with positive or negative outcomes will be important for delineating developmental trajectories of emotional memory for various types of inputs from the environment.

The present study implemented a novel emotional working memory task in conjunction with immediate and 24 hour recognition memory tests in order to examine developmental trajectories of memory processes for emotional information. We show that memory for emotional stimuli, particularly fearful faces, differs across development based on the timescale at which memory is assessed. As shown previously, working memory shows improvements with

age. In contrast patterns of recognition memory begin to differentiate, with greater improvement in memory for fearful faces into adolescence, that stabilizes and increases gradually into adulthood and increased memory for places during adolescence. After a 24 hour consolidation period, enhancements in memory for fearful faces are observed across age. These data suggest that the temporal dynamics of memory processes may shift across development, such that memory gradually becomes more “adult-like” as time is allowed for memory representations to be consolidated. Further investigation of differences in emotional memory and the underlying neural circuitry across development may yield greater insights into how age-related changes in memory processes may drive emotional reactivity—and vice versa— throughout adolescence.

Chapter 5:

Conclusions and Implications: The complex influences of emotions on cognitive and neural processes across development

The preceding chapters aimed to examine the influence of emotions— of both positive and negative valence as well as brief and prolonged duration— on cognitive and neural processes across development. Using a novel behavioral paradigm in conjunction with neuroimaging, the first experiment demonstrated dissociable effects of positive and negative brief and prolonged emotional states on cognitive control that were paralleled by differential recruitment of fronto-parietal and fronto-striatal circuitry in healthy adults (Chapter 2). The second experiment used the same experimental paradigm to reveal a developmental shift in cognitive control in both brief and prolonged negative emotional situations into the early twenties, that coincides with dynamic changes in prefrontal circuitry (Chapter 3). Motivated by the question of how emotional information may impact memory processes during development, the third experiment used a second novel behavioral paradigm to show evidence for developmental changes in the temporal dynamics of working, short term, and long term memory for emotional and non-emotional stimuli (Chapter 4). Together, the experiments described in the previous chapters highlight the importance of considering the influences of emotional context on behavior and brain function across development and suggest that the understanding of emotional influences on cognitive control processes may be bolstered by the study of developmental differences in emotional memory processes.

Effects of emotion on performance and neural activity vary with age, into young adulthood

Consistent with a large body of behavioral, psychophysiological, and neuroimaging research referenced in the preceding chapters, the experiments in this thesis show that emotional inputs influence cognitive control performance and putative neural circuitry differently across age. The current thesis builds upon and extends extant findings in several key ways. The CCUE task implemented in Chapters 2 and 3 introduces a new behavioral paradigm that employs sustained emotional manipulations that are more reliant on experimenter control than subject control. The incorporation of both positive and negative emotions in the CCUE paradigm allows for distinguishing effects of arousal versus valence on both behavior and brain activity. The experimental manipulation of sustained, valenced arousal has been validated through self-report measures of anticipation of positive or negative outcomes and a psychophysiological measure of arousal, although additional data will be needed to validate induced states of emotional arousal as mood states (e.g. Jallais & Gilet, 2010; Kohn et al., 2013; Wagner et al., 2012; Zhang et al., 2014). The mixed block/event-related design allows for assessment of behavior and brain activity in response to sustained states, brief cues, and their interactions. Stimuli and/or anticipated events within the task may be modified to address specific experimental questions, such as those pertinent to special populations (Dreyfuss et al., under revision).

The fundamental developmental question assessed using the CCUE task was whether brief or sustained emotional states impact cognitive control and the

underlying neural circuitry differently in the socially and legally relevant age range of 18 to 21 years-old relative to teens or adults over 21. Adolescents show poorer performance relative to adults under emotional arousal, in line with previous research (Galvan et al., 2006; Hare et al., 2008; Geier et al., 2010; Van Leijenhorst et al., 2010; Somerville et al., 2011; Cohen-Gilbert & Thomas, 2013; Grose-Fifer et al., 2013; Dreyfuss et al., 2014). Similarly to adolescents, young adults show poorer cognitive control relative to adults under negative emotion, both brief and prolonged. Decrements in cognitive control performance were particularly pronounced in response to fearful cues, which signal a potential threat in the environment, with comparable performance in teens and young adults. Diminished performance under brief and prolonged negative emotions in teens and young adults relative to adults was paralleled by differential activity and connectivity of lateral and medial prefrontal cortical systems. Examining age continuously revealed a great deal of individual variability in behavioral and neural responses, indicating that gradual changes occur with development and that there is no obvious demarcation point at which behavior or brain activity could be said to be "mature." On the group level, the results of this experiment suggest a developmental shift in cognitive control under negative emotions that may be a potential behavioral and functional implication of well-documented protracted cortical circuitry development (Gogtay et al., 2004; Mills et al., 2014; 2016; Simmonds et al., 2014; Sowell et al., 1999; Whitaker et al., 2016).

Few empirical studies have homed in on the behavioral and neural development of the late adolescent/young adult age range. Studies of adolescent development typically bin by age groups, often placing individuals

18 and over in the “adult” category (Somerville, 2016), consistent with legal and societal norms. The handful of studies that have investigated social and/or emotional influences on cognitive control in young adults used varying age ranges to define this age group and the results are mixed (Chein et al., 2011; Cohen-Gilbert et al., 2014; Silva et al., 2016; Veroude et al., 2013; Weigard et al., 2014). For example, in separate studies, individuals ages 18 to 22 years old showed little impact of peer presence on decision-making in a simulated driving task (Chein et al., 2011), less delay discounting (preference for immediate smaller rewards over delayed larger rewards) when they believed a peer was observing them (Weigard et al., 2014), and better overall gambling task performance in the presence of peers (Silva et al., 2016). Behavioral differences were not observed in a neuroimaging study of an emotional Stroop task comparing 18 - 19 year-olds to 23 - 25 year-olds, however differential activation of prefrontal cortical circuitry between the two age groups was observed (Veroude et al., 2013), consistent with the findings of the present thesis. In line with the idea that developmental shifts in behavior occur into the twenties, a recently reported international behavioral study of 5000 individuals ages 10 to 30 showed that sensation seeking peaks at age 19 and self-regulation does not plateau until the mid-twenties (Steinberg et al., 2017). Thus, the common takeaway from the extant research, including Chapter 3, is that behavioral and functional brain development continue past 18, the age at which society typically considers individuals to be adults.

Further evidence of the influences of emotion on behavior and brain activity into young adulthood comes from a recent study that also employed the CCUE task. The elements of the task were stripped away and analyses focused on

“brain states” in the sustained emotional contexts using residual patterns of functional connectivity, similar to resting state, in individuals ages 10 to 25 years old. “Brain age” of a participant was predicted using functional connectivity from the neutral condition and validated using structural MRI data. Predicted “brain age” could then be compared to “brain age” in the positive or negative emotional states to assess whether individuals were predicted younger or older in each emotional state. Teens, on average, showed a younger predicted “brain age” under both positive and negative emotional states. Next, the hypothesis that predicted younger or older “brain age” may represent distinct neural phenotypes that might relate to risky behaviors was tested using a self-reported risk perception measure. Across all ages, the “predicted younger” phenotype related to increased risk preference and decreased risk perception. Grouping individuals by legally relevant age groups (13-17, 18-21, and 22-25) as well as those predicted younger or older in each emotional state revealed that young adults with predicted younger “brain age” in emotional states, both positive and negative, show greater risk preference. There were no significant differences in risk preference in either emotional state for adolescents or adults based on predicted “brain age.” This experiment shows that while teens are more likely to show a predicted younger “brain age” under emotional states, young adults predicted younger are more likely to consider the benefits of risks over the costs and may take more risks (Rudolph et al., 2017).

Together, existing empirical studies of late adolescents/young adults show evidence of differences in behavior, brain activity, and functional connectivity in response to social and emotional inputs that differs from that of adults.

Critically, different patterns of behavior and brain activity only seem to emerge in certain social or emotional contexts and there is considerable individual variability in both behavior and brain activity. These results suggest that the young adult age range may represent a developmental window during which individuals may still be particularly sensitive to socioemotional inputs from the environment. Future studies that model age continuously as well as longitudinal studies may help characterize developmental sensitivities during young adulthood. Developmental research examining behavior and brain activity in specific emotional, motivational, and social contexts in which cognitive control may be liable to breakdown will help establish normative developmental trajectories of behavior and neural circuitry under different environmental circumstances. Concurrent assessment of how individual variability in emotional and behavioral traits may contribute to cognitive control processes across age may help to identify characteristics of individuals who are particularly prone to lapses or increases in cognitive control.

Temporal dynamics of memory for emotional and non-emotional stimuli may be changing across development

The preliminary data presented in Chapter 4 suggest that age-related differences in memory for emotional and non-emotional items vary based on when memory assessed. Working memory improved linearly across development, short term memory showed a cubic age-related pattern, and long term memory did not vary with age. Working, short term, and long term memory processes each varied based on stimulus type. Memory under low load was uniform across age for neutral faces and places, but showed

increases for happy and fearful faces. Working memory under higher load showed linear increases across stimulus type, but better working memory across age for faces versus places. Short term memory in an immediate recall group showed similar cubic patterns for neutral and happy faces, such that memory improved into adulthood. However, memory for places and fearful faces showed significantly different patterns, such that short term memory for places peaked in adolescence while short term memory for fearful faces initially showed rapid improvement into mid-adolescence, followed by gradual improvement into adulthood. Finally, long term memory in a 24 hour recall group was increased for fearful stimuli across age. These findings suggest that both the time of assessment and the type of stimulus influence memory processes across development.

The diverging patterns of short term memory observed for place and fearful face stimuli may provide developmental insights rooted in evolutionary history. Although the enhanced memory for places during adolescence may be a consequence of the structure of the behavioral paradigm (see Chapter 4 Discussion), the observed boost in memory could also be indicative of an adolescent specific effect. The latter is supported by the fact that memory gains are not observed for individuals in their mid-twenties and we might expect a finding that is an artifact of the task to be observable across ages. It may be advantageous for individuals to show better short term memory for different settings during the transition to adulthood as this is a time of exploration when individuals often encounter new environments as they transition to independence and eventually moving away from the home (Casey et al., 2010; Casey, 2015). Better memory for places in the short term may aid

in dynamic exploration and navigation through different settings or environments. Supposing that the boost in memory for places is an artifact of the task that is specific to adolescents, this result may suggest that adolescents show better memory in the short term for novel stimuli. An adolescent specific novelty bias could also be related to facilitating exploration and comparisons of novel settings that individuals may encounter during this transitional period of development.

In contrast to the adolescent specific pattern of improved short term memory for places, short term memory for fearful faces shows an adolescent emergent pattern with gradual gains in memory into adulthood. The comparatively rapid gains in short term memory for cues of potential threat in the environment, relative to neutral or happy cues, from childhood to adolescence may reflect the importance of remembering these cues during times of increasing independence relative to periods of development when a caregiver is present and provides protection. Memory for cues of potential threat may be important in the short term due to dynamic exploration of new environments that will generally not take place in the presence of a caregiver, with adolescents typically returning to the safety of home in between bouts of exploration, until a new home is established in adulthood. Following consolidation over a 24 hour period, fearful faces are enhanced in memory, irrespective of age, suggesting that the evolutionary advantage of retaining cues that indicate a potential threat in the environment in long term memory may transcend the caregiver's role in providing safety (Gee, 2016) in more immediate situations, potentially giving the organism a chance to recognize and perhaps even avoid possibly threatening situations across age.

Replication of the findings in Chapter 4 is warranted and further experiments in examining episodic memory processes across development will be necessary to clarify the influence of emotional, social, and novel information on memory processes across development. Neuroimaging studies using paradigms such as the one described in the previous chapter will help to elucidate the neural mechanisms of developmental changes in memory and how imbalances in structural development of brain areas implicated in emotional memory (see Chapter 4 Introduction and Discussion for review) may lead to differences in circuit function that may influence memory for specific cue types at different timescales. A related area of study that may yield important developmental insights linking changes in emotional memory to changes in behavior is the study of emotional learning and memory for emotional learning. The experimental paradigm presented in Chapter 4 did not include a learning component, which may lead to different patterns of emotional memory than those observed in the present study.

Emotional learning and memory have most commonly been studied using fear conditioning. Developmental studies of fear conditioning have primarily been carried out in rodents (Shechner et al., 2014). A particularly striking developmental finding is that of temporary suppression of contextual fear memory during adolescence in mice, which can subsequently be retrieved in adulthood (Pattwell et al., 2011). Temporary suppression of contextual fear memory is thought to be due to changes in hippocampal-amygdala communication, resulting in blunted amygdala activity during adolescence, in contrast to an imbalance in prefrontal-amygdala circuitry, resulting in

heightened amygdala activity, thought to underlie attenuated cued fear extinction during adolescence (Casey, 2015; Pattwell et al., 2012). A study in mice aimed at reconciling these two divergent findings shows that dynamic remodeling amygdala-hippocampal-mPFC circuitry is associated with changes in behavior during adolescence and that targeting components of amygdala-hippocampal-mPFC circuitry via behavioral interventions can lead to changes in long-term fear memory expression (Pattwell et al., 2016). Together, these studies suggest that developing emotional learning and memory processes can differentially affect behaviors, both in the short and long term. Further characterization of developmental trajectories of emotional learning, memory, and underlying neural circuitry will be informative for determining the interplay between learning, memory, and cognitive control across development.

A unique developmental sensitivity to negative emotions

While adolescence is often conceptualized as a time of sensitivity to rewards, full of excitement and thrills, the data in the current thesis emphasize that negative emotions can also impact cognitive and neural processes throughout adolescence. In particular, the present thesis highlights developmental differences in response to potential threat. The results of the experiments presented in the previous chapters show effects of both brief and prolonged potential threat on cognitive control and underlying neural circuitry in adolescents and young adults as well as effects of cues of potential threat on episodic memory processes across development. The way individuals detect, process, remember, and ultimately react to potential threats in the

environment might impact survival, thus the findings described in the previous sections may have an evolutionary basis.

As described in the previous section, the transition into adulthood is filled with new experiences and exploration of new environments. Adolescents have been proposed to show attenuated sensitivity to aversive properties of stimuli, which may motivate them towards action when faced with negative emotional stimuli (Doremus-Fitzwater & Spear, 2017). Attenuated aversions would help to facilitate exploration, even when faced with aversive inputs from the environment, which is crucial for gaining new experiences and eventually establishing independence from the caregiver. While adolescents may be more capable of tolerating aversive properties of stimuli, the data in the present thesis also suggest increased vigilance and better memory for potential threats. Heightened vigilance and memory for cues that indicate potential threats would serve to promote survival by enhancing awareness of possible dangers that may be present while exploring new environments (Casey, 2015). Together, overcoming aversive properties of the environment while remaining vigilant and storing cues that may indicate threat in memory would help to promote healthy, adaptive development. However, developmental sensitivities to negative emotions, which might show interindividual variability, may also be related to increased prevalence of anxiety and stress related disorders during adolescence (Hartley & Casey, 2013). The implications of the experiments described in the present thesis will be further discussed with respect to mental health, social, and legal policy in subsequent sections.

Implications for models of adolescent neurobiology

The prominent neurobiological models of adolescence all recognize asymmetric and dynamic changes in developmental trajectories of limbic and prefrontal circuitries as probable neurobiological mechanisms underlying adolescent behaviors (Steinberg, 2005; Ernst et al 2006; Casey et al., 2008), which is a premise supported by a multitude of developmental science research (e.g. Monk et al., 2003; Galvan et al., 2006; Hare et al., 2008; Geier et al., 2010; Van Leijenhorst et al., 2010; Somerville et al., 2011; Cohen-Gilbert & Thomas, 2013; Grose-Fifer et al., 2013; Dreyfuss et al., 2014; Gee et al., 2014; Heller et al., 2016). The experiments in the current thesis suggest several refinements to the existing models that may be useful additions to the conceptualization of adolescent neurobiology and the behavioral implications. Chapters 2 and 3 support recent work highlighting the importance of within and between network connectivity (Gu et al., 2015), particularly amongst cortical networks involving the prefrontal cortex (Crone & Steinbeis, 2017), in contributing to the development of cognitive processes. Chapter 4 supports a recent proposal (Murty et al., 2016) of the integration of hippocampally-mediated learning and memory processes into existing conceptual frameworks of how social, emotional, and motivational information may influence cognitive control throughout adolescence. This section will describe proposed refinements in further detail, drawing from both conclusions of experiments in the current thesis and recent developmental research.

While much of the focus of adolescent neurobiological models has been on the development of subcortical-subcortical and subcortical-cortical connections

highlighted by the imbalance model (Casey et al., 2008; Casey, 2015), recent elaboration of the imbalance model (Casey et al., 2016) and emerging empirical work suggests that imbalances within and between cortical circuitries may be a crucial component of changes in cognitive control behaviors into late adolescence/young adulthood. Studies of neurocircuitry function in rodents show that major functional changes take place within the circuits of the PFC during adolescence. Adolescence is a time of major remodeling of both pre- and postsynaptic glutamatergic and GABAergic signaling, which is modulated in large part by dopamine and cannabinoids (Caballero et al., 2016). D1 receptor expression does not reach adult levels in the PFC until late adolescence (Flores-Barrera et al., 2014; Tseng & O'Donnell, 2007), thus it is hypothesized that the transition into adulthood may be a critical phase for refinement of dopamine-dependent neurotransmission (Caballero et al., 2016). Endocannabinoid receptor and ligand levels also show major changes in PFC over the course of development, with most studies pointing towards enhanced endocannabinoid signaling during adolescence that can influence glutamatergic, GABAergic, and dopaminergic signaling (Doremus-Fitzwater & Spear, 2016; Fitzgerald et al., 2012). Developmental changes in neurotransmission are thought to underlie changing behavior throughout adolescence, although further work linking neurochemical and microcircuit-level changes to behavior is needed (Doremus-Fitzwater & Spear, 2016). The PFC in rodents is often described as a single region or is subdivided into prelimbic and infralimbic cortex, limiting the potential extrapolations of these data to humans. Nonetheless, these data provide evidence of significant functional remodeling of connections within the PFC during adolescence that may have important implications for behavior.

Several recent studies of functional connectivity in humans across adolescence support the idea that ongoing functional organization of cortico-cortical connections involving the prefrontal cortex may be critical to the development of cognitive control processes. Analysis of resting state connectivity shows that the largely cortical default mode network begins to play a major role in facilitating connections between other neural systems during adolescence and that between network connectivity of various neural systems with the default mode network is correlated with a general measure of cognitive performance across age (Gu et al., 2015). A contemporaneous study of diffusion MRI shows significant remodeling of brain network hub connectivity—such that connectivity of frontal hubs with both subcortical and cortical hubs becoming particularly prominent— in late adolescence (Baker et al., 2015). These results are paralleled by the aforementioned study of emotional “brain age,” as the key nodes of functional neuroanatomy associated with age prediction were mostly cortical regions, including the vmPFC, dmPFC, and mPFC regions of the default mode network (Rudolph et al., 2017). A study of age-related differences in emotion regulation further showed that inverse vmPFC-amygdala coupling is associated with age and that vlPFC activity is also associated with the vmPFC-amygdala relationship, implicating vlPFC interactions with the vmPFC in better age-related negative affect regulation (Silvers et al., 2016). Together, these studies suggest that cortical network remodeling involving the PFC may be important for the development of cognitive control, especially in emotional contexts.

Chapter 3 of the current thesis describes age-related differences in lateral and medial prefrontal activity and connectivity that emerge in negative emotional contexts. Although lateral and medial prefrontal cortex are each composed of subregions, the broad lateral and medial divisions of PFC are implicated in different contributions to behavior, neural computations, and neural networks. Lateral PFC is implicated in behavioral regulation, including cognitive control (Tanji & Hoshi, 2008, Vincent et al., 2008) and affective regulation (Silvers et al., 2015; Wager et al., 2008) processes, and as a component of the fronto-parietal and cingulo-opercular networks (Power et al., 2011). Medial PFC is implicated in self-referential thought, integration of affective information, affective computations and regulation (Roy et al., 2012), and is a component of the default mode network (Power et al., 2011). Medial PFC has reciprocal connections with subcortical regions, thus it has been proposed that lateral PFC systems regulate cortico-subcortical and subcortico-subcortical systems via cortico-cortical connections with the medial prefrontal circuitry (Casey et al., 2016; Silvers et al., 2016). A recent review of models of cognitive control in childhood and adolescence suggests that models of the developmental neurobiology of cognitive control can be further refined by taking into consideration the putative computations performed by different subregions of PFC, particularly dorsolateral versus medial PFC, and the development of connectivity between subregions (Crone & Steinbeis, 2017). While defining developmental profiles of each subregion of the PFC is likely beyond the scope of a single model—a recent multi-modal parcellation of human adult cortex suggests that mPFC and dlPFC alone can be subdivided into approximately 28 subregions (Glasser et al., 2016)—incorporating a broad framework describing the protracted development of cortico-cortical

interactions (Casey et al., 2016) may paint a more complete picture of adolescent neurobiology.

A neurocognitive system that has yet to be fully conceptually integrated with current neurobiological accounts of adolescence is the hippocampally-based memory system and its communication with prefrontal cortical and limbic subcortical systems. The imbalance model has suggested that the hippocampus plays an important role in adolescent neurobiology by highlighting the critical function of hippocampal projections to the amygdala and PFC providing contextual information that influences fear memory and extinction memory in fear conditioning paradigms across species (Casey, 2015). The current thesis suggests that episodic memories for emotional and non-emotional cues show different age-related patterns when working, short term, and long term memory are assessed. While we have proposed that the observed changes in memory processes may be due to imbalances in development of neural circuitry implicated in emotional and declarative memory, further studies examining emotional memory processes in conjunction with neuroimaging are necessary to gain a better understanding of how neural memory systems may be interacting differently across age.

The hippocampus appears to show regional volumetric changes across adolescence (Daugherty et al., 2016; Gogtay et al., 2006; Tamnes et al., 2014), similar to protracted development cortical regions such as the PFC (Gogtay et al., 2004; Simmonds et al., 2014; Mills et al., 2016). The protracted structural development of hippocampal and cortical regions suggests that functional maturation of circuits involving the hippocampus and PFC may

continue into young adulthood. While studies of fear conditioning, primarily in rodents, clearly indicate a consequential role for memory systems involving hippocampus-amygdala-mPFC circuitry in behaviors expressed both in the short and long-term, there has been little empirical work investigating how memory systems may interact with cognitive control systems across development in humans.

A recently proposed model of cognitive development during adolescence posits that interactions between memory and executive systems, supported by the hippocampus and PFC and modulated by mesolimbic dopamine, are crucial for supporting goal-directed behaviors (Murty et al., 2016). Specifically, the integration of previous experiences with the present situation is proposed to be particularly important in guiding behavior. Given that heightened sensitivity to emotional inputs during adolescence is associated with reactive behaviors in the heat of the moment, it seems perhaps more compatible to suggest that memory and control processes interact bidirectionally and synergistically to facilitate adaptive behaviors across development. That is, prior experiences with different stimuli in different contexts may influence behavior and behavior in response to different stimuli in different contexts may influence memory. Learning would seem to rest at the intersection of cognitive control and memory processes, with emotional learning enabling the prediction of motivationally salient events and reflexive deployment of physiological and behavioral responses that are refined over time.

Together, these minor refinements to concepts already set forth by the imbalance model of adolescent neurobiology (Casey, 2015; Casey et al.,

2016) further integrate cortical networks and active learning and memory processes into this circuit and action-based account of cognitive development. Evidence of structural and functional development of the neurocircuitry implicated in cognitive processes into young adulthood suggests that behavioral implications of protracted development, such as the emergent findings reported in the current thesis, should be observable. Another nuanced inference that arises from further highlighting a role for learning and memory systems in the neurobiology of cognitive development is the increased emphasis on the ongoing interactions between the biological and experiential components of development (Byrge et al., 2014; Karmiloff-Smith, 2009). Development is a dynamic process involving cascades of neural and behavioral changes (Casey et al., 2016; Masten & Cicchetti, 2010) that can be influenced not just in the moment but also in the long-term by environmental inputs, particularly by salient social, emotional, and/or motivational inputs. Differences in both life experiences and the way that life experiences are processed and stored in memory may account, in part, for the heterogeneity observed in both behavior and activity of neural systerms across development. Thus, models of adolescent neurobiology can be characterized by imbalances and integration of neural circuitry, shaped by environmental inputs and experiences in novel environments.

Implications for mental health policy

The World Economic Forum has reported that mental illnesses are the largest cost drivers of non-communicable diseases at an estimated $2.5 trillion in global costs in 2010 and projected cost of $6 trillion by 2030 (WHO, 2007).

Roughly half of all Americans are predicted to meet criteria for a mental health disorder at some point in their lives (Kessler et al., 2005). Approximately 75% of the first onsets of mental illness occur by the mid-20s, with 25% of the first onsets occurring in the late teens to mid-twenties (Kessler et al., 2007). Moreover, psychiatric illness is the strongest risk factor for suicide (Moscicki, 2001), which is the third leading cause of death in young people ages 15 to 24 (CDC, 2010). These epidemiological data highlight the importance of understanding basic behavioral and neural developmental trajectories through young adulthood as a step towards identifying routes for potential early interventions that will improve outcomes and ultimately reduce the economic burden placed on society.

Emotional dysregulation—both cue triggered and on sustained timescales— is a core feature of most mental illnesses (Hofmann et al., 2012; Gross & Jazaieri, 2014). Adolescents' increased emotional reactivity and poorer cognitive control in emotional contexts may contribute to the increased prevalence of mental illness during this transitional period of development (Merikangas et al., 2010; Lee et al., 2014). The findings presented in the current thesis suggest developmental sensitivities to negative emotional information, into young adulthood. Chapter 3 provides evidence that young adults' behavioral performance and brain activity is influenced by negative emotions, both brief and prolonged, similarly to adolescents. Negative emotions and their impact on cognitive control behaviors are relevant to core features of internalizing (anxiety and mood disorders) and externalizing disorders (such as conduct and attention-deficit hyperactivity disorders) that are prevalent in young people (Merikangas et al., 2010). Furthermore,

impulsivity in the context of negative emotions is higher in individuals with suicidal ideations and in those who attempt suicide (Klonsky & May, 2010). Thus, the behaviors occurring in negative affective states may be maladaptive and even, as underscored by the extreme case of attempted suicide, highly detrimental to the individual. Further studies of the development of behavioral regulation in various emotional, social, and motivational contexts and the neural correlates into young adulthood may provide important insights into disorders that commonly emerge in adolescence or young adulthood, such as substance abuse and mood disorders (Kessler et al., 2005; 2007).

Developmental changes in emotional learning and memory processes may also contribute to increased vulnerability to mental illnesses during the transition to adulthood. Chapter 4 provides evidence for accelerated improvements in short term memory for negative emotional cues with age and enhanced long term memory for negative emotional cues across age. The prioritization of negative emotional items in memory may serve as a catalyst for dysregulation of negative emotions. While perturbations in emotional learning and memory processes exist in a number of different mental disorders (Harvey et al., 2014; Morris et al., 2014), perhaps the most well studied paradigm is fear conditioning, which serves as an experimental model of the cognitive processes that elicit the reflexive physiological and behavioral responses characteristic of anxiety disorders (LeDoux & Pine, 2016). As described in previous sections, there are marked changes in fear learning and memory that emerge during adolescence. Vulnerability to anxiety or stress-related disorders may be conferred by individual differences in the neurocognitive structure of fear conditioning. Some individuals may update a

learned fear memory with safety information during fear extinction, whereas other individuals may form a new memory during extinction, leaving the original fear memory intact, leading to increased spontaneous recovery of the fear response (Gershman & Hartley, 2015). While the neural mechanisms and developmental trajectories of such individual differences have yet to be studied, the delineation of individual variability in emotional learning and memory processes may offer important insights into neurocognitive factors that influence risk and resilience to psychiatric disorders.

Ongoing behavioral and brain development throughout adolescence into young adulthood presents an opportunity to better understand the etiology of mental illnesses and possible avenues for early intervention and treatment as steps toward reducing the burden of mental illness on individuals and society (Lee et al., 2014). Aligning with the focus on emotional influences on cognitive processes in the present thesis, researchers and clinicians have suggested that tailoring psychotherapeutic interventions to concentrate on building emotional regulation (Moyal et al., 2015) and learning and memory (Harvey et al., 2014) strategies may improve the effectiveness of these treatments. Developmental neuroscience research may shed light on key timepoints and specific contexts over the course of development when interventions or treatments may be the most, or the least, efficacious (Suleiman & Dahl, 2017) and may delineate developmental trajectories of individual differences that have implications for identifying individuals who may be most vulnerable to progression to a clinical disorder. Acquiring a more comprehensive understanding of the normative development of neurocognitive processes is a crucial step towards uncovering potential neurobiological and behavioral

markers of pathological dysregulation, particularly in response to emotions or in emotional states, that may be important for early identification of psychiatric disorder and in assessing outcomes of interventions across development.

Implications for social and legal policy

Age-related social and legal policies, from age of jurisdiction to legal ages of purchasing controlled substances to eligibility for social and financial support, have historically been based on political considerations and conventional wisdom rather than empirical evidence. The past twelve years have brought about several landmark US Supreme Court decisions citing developmental science to make the case for differential treatment of juvenile and adult offenders in the criminal justice system (Cohen & Casey, 2014) signaling a potential shift towards evidence-based policymaking, at least with respect to the treatment of young people. Much of the existing work informing juvenile justice policy has relied on psychological rather than neuroscientific evidence, with psychologists and legal scholars collaborating to describe potential juvenile justice policy implications of developmental differences in behavior (e.g., risk taking, sensation seeking, impulsivity). While neuroimaging techniques are not presently capable of supporting arguments for or against the guilt or innocence of defendants, developmental neuroscience research allows for suggestions of potential neural mechanisms that may explain the unique behavioral patterns observed across development and therefore complements psychological research by providing converging evidence for developmental phenomena.

While a substantial body of work has focused on the adolescent age range, most often defined as ages 13 to 17, less research has focused on the late adolescent/young adult age range. The young adult age range is of particular legal and social relevance as it is the timeframe in which, for different intents and purposes, an individual begins to be considered an adult in our society (Cohen et al., 2016). The current thesis provides evidence that, similar to teens, young adults age 18 to 21 show diminished cognitive control relative to slightly older adults in threatening situations that is paralleled by differential activation of lateral and medial prefrontal circuitry. This pattern of diminished performance was not observed in a neutral condition and young adults actually shows more similar behavior and brain activation to adults than to teens when presented with positive social cues (smiling faces). These data highlight the importance of considering influences of emotional context on brain and behavior when evaluating age-related legal and social policies.

Justice centers and programs have already begun to recognize young adults as a unique transitional age group, typically defined as ages 18 to 24, in large part due to developmental neuroscience evidence showing continued brain maturation well into the 20s (Institute of Medicine & National Research Council, 2014). However, the treatment of young adults in the system is often unpredictable. While individuals 18 and older, and oftentimes individuals even younger, are typically referred to the adult justice system, young adults can technically be under the jurisdiction of both the juvenile and adult justice systems for the purposes of supervision and services. The lack of defined roles for either system can lead to lapses in necessary services, such as health care, education, and general welfare, for young adults (The Council of

State Governments Justice Center, 2015). Another complexity in the treatment of young adults in the system is that this age range shows significantly higher rates of recidivism compared to other age groups, with one study finding that 84% of individuals released under the age of 25 were rearrested within five years (Durose et al., 2014). Due in part to the fact that research on young adults has thus far been limited, policymakers have yet to reach a clear consensus on how to best serve this age group in order to reduce recidivism and improve outcomes (Institute of Medicine & National Research Council, 2014; The Council of State Governments Justice Center, 2015).

The influence of emotions on brain and behavior into young adulthood is also of particular relevance to the criminal justice system given the prevalence of mental illness amongst those in the system, especially amongst youth. Approximately 70% of incarcerated juveniles and 50% of incarcerated adults have a diagnosable mental illness (James & Glaze, 2006; Meservey & Skowyra, 2015). Many of these individuals, especially the young adults, have a co-occurring substance use disorder. Amongst juveniles, nearly 30% of disorders lead to serious impairments in functioning (Shufelt & Cocozza, 2006). Mental health considerations are further complicated by traumas experienced, predominantly by younger inmates, during previous incarcerations for which individuals typically do not receive treatment (The Council of State Governments Justice Center, 2015). Results from Chapter 4 of the current thesis together with previous work both in humans and rodents suggests enhanced, persistent memory for negative emotional events, which may be exacerbated if individuals remain in the prison system environment. This unfortunate reality further underscores the importance of understanding

neurocognitive processes in negative emotional states, which are frequently encountered when incarcerated, across development. Research focusing on the influences of negative emotions on behavior and brain activity across development can serve as a step towards further highlighting to policymakers the potentially detrimental effects of negative emotional experiences on the developing brain and aiding in identifying ways to mitigate the harmful consequences for young people in the system.

The justice system's recognition of juveniles and young adults as developmental populations that fundamentally differ from adults offers the implicit recognition that the brain does not mature in isolation but rather is fine-tuned with experiences and learning. Learning occurs both by doing and by observing. Opportunities to engage in active learning and to master the skills necessary to successfully transition into independent adulthood are dramatically reduced and influenced by experiences of incarceration. This is not to suggest that teens and young adults should not be held accountable for their actions, but rather that diminished responsibility in specific contexts during this transitional period of development may be considered in sentencing, punishment, and rehabilitation. Further justice system reforms related to the treatment of juveniles and young adults should create more opportunities to engage in prosocial interactions in the community and to have prosocial role models in order to alleviate the potentially harmful effects of negative emotional experiences inherent to the criminal justice system. This approach to future reforms may be useful for bolstering healthy development and may help improve long-term outcomes as young people leave the system and become members of society. As developmental science continues to shed

light on how different experiences, situations, and environmental inputs impact brain and behavior, the results of developmental research may be pertinent to future court rulings and policy decisions regarding the treatment of juveniles and young adults in the criminal justice system.

Future directions

The ability to learn from and remember salient information in the environment is essential for an individual to survive and thrive throughout the lifespan. A burgeoning idea in the current thesis is that emotional information in the environment may influence the capacity to learn and remember across development. Developmental differences in emotional learning and memory may in turn show a synergistic relationship with behaviors in response to emotional information. Studies of classical conditioning have shown that, as individuals track the dynamic state of the world around them, the emotional significance of a cue, and therefore the behavioral responses to the cue, can fluctuate as the statistics of the environment change (Phelps & LeDoux, 2005; Milad & Quirk, 2012; Dunsmoor et al., 2015). Studies of fear learning reviewed earlier in this chapter suggest that normative developmental changes in neurocognitive processes may cause emotional learning and memory to become more persistent, exerting greater influence over subsequent behavior, or to become suppressed, exerting little immediate influence on behavior, during adolescence. Although there exists a rich literature on how emotional information, can drive immediate responses and actions across development (e.g. Hare et al., 2008; Geier et al., 2010; Somerville et al., 2011; Cohen-Gilbert & Thomas, 2013; Grose-Fifer et al., 2013; Dreyfuss et al., 2014; Heller

et al., 2016), few studies have considered developmental changes in the neurocognitive structure of emotional learning, how developmental differences may influence the persistence of emotional information in memory, or how individual variability in emotional learning may alter developmental trajectories of memory processes.

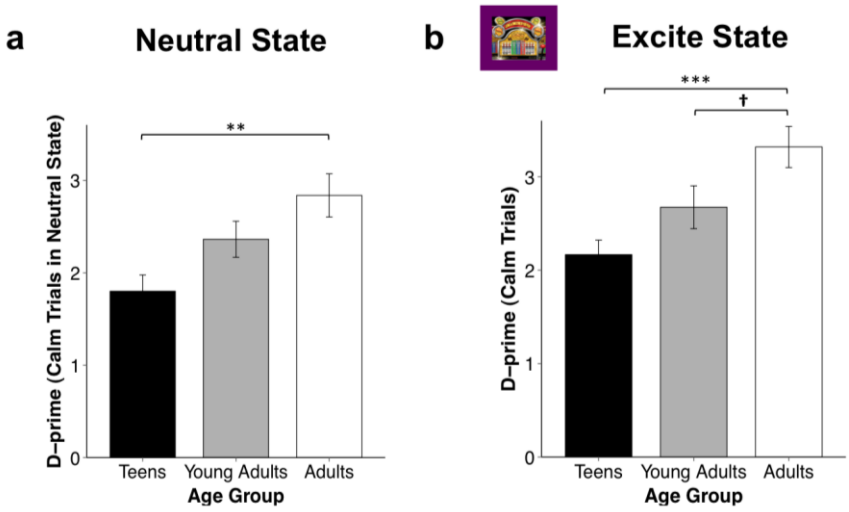
Recent work highlights qualitative differences in the cognitive representations that can be formed during dynamic emotional learning, specifically during fear conditioning (Gershman et al., 2010; Gershman & Hartley, 2015). Whereas for some, memories of fear learning may be eroded by neutral experience, for others, learned fear may persist in memory, remaining capable of influencing subsequent behavior. Such differences can be captured using computational models of classical conditioning, informed by behavioral neuroscience research in both animals and humans (Gershman et al., 2010; Gershman & Hartley, 2015; Dunsmoor et al., 2015). Although recent studies suggest pronounced changes in both positive and negative emotional learning and memory processes across development (Baker & Richardson, 2015; Davidow et al., 2016)**,** little is known about how variation in emotional learning emerges developmentally, at both the behavioral and neurobiological levels, and how these changes in the cognitive structure of affective associations may modulate subsequent memory of episodic details in the environment.

Experiments addressing these research questions lie at the intersection of developmental, affective, and computational cognitive neuroscience. An integrated program of research would begin to address how emotions influence learning, memory, and underlying neural processes by investigating:

1) developmental trajectories of individual variability in the neurocognitive structure of emotional learning, both positive and negative, 2) the potential utility of computational models that capture variation in learning processes in forming predictions about engagement of neural circuitry underlying emotional learning across development, and 3) how individual differences in emotional learning may influence memory for items presented during learning. This program of research will begin to elucidate how heterogenous developmental changes in the lability or persistence of emotional learning in memory may render previous emotional experiences capable of shaping subsequent behavior. Studying individual variation in emotional learning and memory across development may provide insights into characteristics that make someone vulnerable to mental illness. By leveraging computational modeling, neuroimaging, psychophysiological, and behavioral approaches to better understand developmental changes in how individuals learn and remember the structure of the emotional environment, these future research directions build upon themes of the current thesis and may shed light on the neurocognitive processes underlying emotional learning and memory that may promote the healthy development of motivated behavior.

APPENDECIES

Appendix 1. Supplemental Results, Chapter 3



Supplemental Fig. S1. Behavioral performance as indexed by d-prime in the a) neutral state and b) excite state.

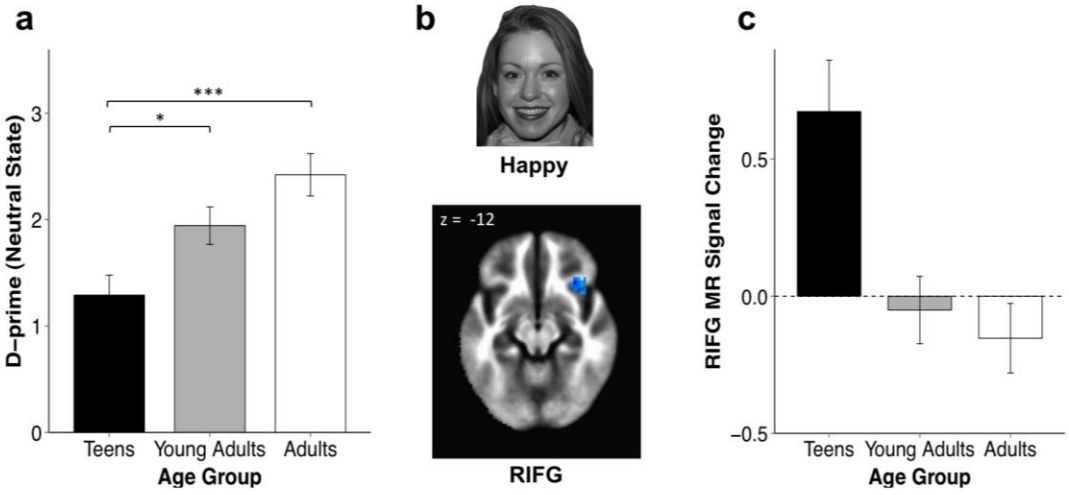
Behavioral Results

We tested the complete, repeated measures model (including all states and cues) and while there was a main effect of age group ($F_{(2,98)} = 15.09$, $p < .001$, $\eta_p^2 = .23$) and an emotional state by emotional cue interaction ($F_{(4,392)} = 4.37$, $p = .004$, $\eta_p^2 = .04$), there was no significant interaction of state and cue with age group ($F_{(8,392)} = 1.39$, $p = .199$).

To test whether race, IQ or socioeconomic status could account for the reported findings, we also ran age group analyses controlling for race, performance IQ, and maternal education. One-hundred and five of the 110 subjects had performance IQ and maternal education information available. The main effects of age group remain significant for performance to fear cues

($F_{(2,80)}$ = 9.49, p < .001, η_p^2 = .11), happy cues ($F_{(2,80)}$ = 8.42, p < .001, η_p^2 = .13), calm cues in neutral ($F_{(2,80)}$ = 6.81, p = .001, η_p^2 = .11), threat ($F_{(2,80)}$ = 16.60, p < .001, η_p^2 = .28), and excitement ($F_{(2,80)}$ = 7.99, p < .001, η_p^2 = .16).

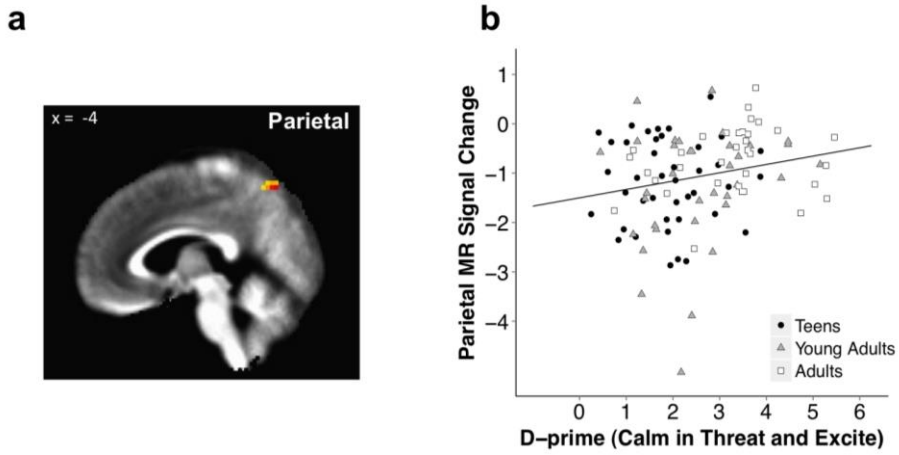
Imaging Results



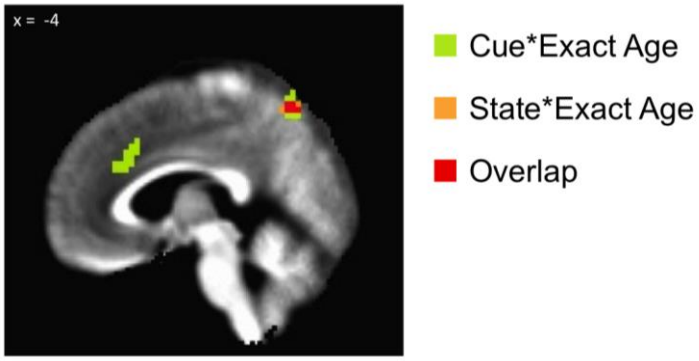
Supplemental Fig. S2. (a) Behavioral performance as indexed by d-prime to (b) happy cues. Diminished behavioral performance in teens was paralleled by increased activity in (b,c) right inferior frontal gyrus (RIFG). Means ± s.e. presented. * = p < .05, ** = p < .01 ***= p < .001

Happy Cues. In parallel to the behavioral results in this emotional condition, we constructed a general linear test in the group linear mixed-effects emotional cue model to compare brain activity of teens to that of adults and young adults, relative to implicit baseline, in response to the happy cues. We found a single cluster that survived whole brain correction, showing more activity in teens than both young adults and adults: the right inferior frontal gyrus (x = -32.5, y = -24.5, z = -11.5, Z = -4.18, cluster: 30 voxels, p < .02, corrected, Figure S3b and S3c). This is consistent with prior work showing

greater RIFG activity for correct trials corresponding with poorer performance



Supplemental Fig. S3. (a) Parietal activation identified in the emotional state by continuous age analysis. (b) Sustained BOLD activity in the parietal cortex under threat and excitement was positively correlated with behavior across age.



Supplemental Fig. S4. Parietal activations in the emotional cue by continuous age analysis (green), the emotional state by continuous age analysis (orange), and the overlap (red).

Conjunction Analysis. A conjunction analyses was performed to examine the degree of overlap of the parietal regions identified in the emotional cue by continuous age and emotional state by continuous age analyses. Activation maps at an individual voxel threshold of $p = 0.005$ were used for the analysis (Figure S4).

Table S1. Emotional Cue by Continuous Age Activation Map

Region	Brodmann's area	Peak Coordinate	Voxels, n	*F*-stat
dACC	24	+0.5, -27.5, +24.5	57	9.45
R Parietal	7	-2.5, +68.5, +54.5	48	9.59
R Cerebellum		-14.5, +62.5, -32.5	34	10.01
L Cerebellum		+18.5, +59.5, -50.5	31	10.06

Cluster FWE corrected $p < 0.05$, individual voxel threshold 0.005, size ≥ 27 voxels

Table S2. vmPFC Functional Connectivity Activation Map (Teen + Young Adults > Adults)

Region	Brodmann's area	Peak Coordinate	Voxels, n	*Z*-stat
R Parietal	40	-29.5, +50.5, +30.5	269	-4.56
R PFC	6,9	-38.5, -0.5, +36.5	152	-4.07
R IFG/Insula	47,13	-23.5, -21.5, -5.5	72	-4.30
L Caudate		+21.5, -6.5, +21.5	65	-4.28
L Cerebellum		+30.5, +59.5, -44.5	61	-4.85
R dACC	32	-5.5, -30.5, +24.5	39	-3.68
R Cingulate	31	-5.5, +29.5, +39.5	39	-4.33
R Cingulate	23	-8.5, +14.5, -33.5	32	-4.20
L Precuneus	7	+15.5, +62.5, +36.5	27	-4.06

Cluster FWE corrected $p < 0.05$, individual voxel threshold 0.005, size ≥ 27 voxels

Appendix 2. Additional Tables, Chapter 3

This appendix provides additional details about the community sample at each site (see Table A1) Both site and sex were covariates in our original design because the data reported are from community samples from two sites (Los Angeles and New York City), one of which had fewer subjects and proportionately more teens and females than the other. Because site contributed significantly to the variance and sex is a legally relevant variable (males have more encounters with the law and justice system than females do), we included both covariates as variables of interest rather than as simple regressors, thereby reducing the degrees of freedom in our model. Treating either or both of these variables as simple regressors did not affect the pattern of statistical significance of our results (ps < .005, η_p^2s $\geq$ .1).

Tables A2 through A6 provide complete details for the five originally planned analyses of variance assessing the effects of emotional cues in the neutral state and calm cues in the emotional states on participants' accuracy (d'). In addition, Table A7 provides statistical results for a full model testing the effects of all variables and their interactions on accuracy. This model includes interactions of simultaneous and opposing positive and negative emotions (e.g., fearful cues when participants were in a state of excitement), although these interactions were not the focus of the study. In this analysis, the pattern of results for the effects of potential threat (fearful cues) are similar to those

reported for our planned comparisons. Specifically, there is a significant Age Group × Cue Type interaction, $F(4, 196) = 2.99$, $p = .02$, $\eta_p^2 = .053$ across the three emotional states (positive, negative, and neutral); cues of potential threat affected cognitive-control capacity similarly in teens and young adults relative to adults over age 21—teens versus adults: $t(63.15) = 4.48$, $p < .001$, $d = 1.04$; young adults versus adults: $t(66.79) = 3.66$, $p < .001$, $d = 0.88$; teens versus young adults: $t(66.28) = 0.41$, $p > .250$, $d = 0.09$. The interaction of age group and sustained emotional state across all three types of emotional cues (positive, negative, and neutral) was not significant for this model, $F(4, 196) = 1.58$, $p = .18$, $\eta_p^2 = .022$. The interactive effect of simultaneous and opposing positive and negative emotions on cognitive control is peripheral to our scientific question and hypotheses, but nonetheless equally interesting.

Table 1. Sex and Age Distributions of the Participants at Each Site

Characteristic	Teens (n)	Young adults (*n*)	adults (*n*)	Total
		Los Angeles		
Female (*n*)	12	6	6	24
Male (*n*)	7	6	5	18
Total	19	12	11	42
Mean age (years)	16.47 (1.14)	19.85 (1.18)	23.59 (0.95)	19.30 (3.14)
		New York City		
Female (*n*)	11	11	11	33
Male (*n*)	11	12	12	35
Total	22	23	23	68
Mean age (years)	15.96 (1.23)	19.90 (1.07)	24.31 (1.02)	20.12 (3.60)

Note: Standard deviations are given in parentheses.

Table 2. Analysis of Variance Testing the Main Effect of Age Group on Performance (d') When Participants Received Fearful Cues and Were in the Neutral State

Effect	*df*	*F*	*p*	η_p^2
Main effects				
Age group	2, 98	11.11	< .001	.164
Sex	1, 98	0.59	> .250	.011
Site	1, 98	12.83	< .001	.119
Interactions				
Age Group × Sex	2, 98	0.99	> .250	.021
Age Group × Site	2, 98	0.90	> .250	.018
Sex × Site	1, 98	1.32	> .250	.013
Age Group × Sex × Site	2, 98	0.54	> .250	.011

Note: The mean value of d' was 1.52 (*SE* = 0.15) for teens, 1.65 (*SE* = 0.17) for young adults, and 2.54 (*SE* = 0.20) for adults. The mean value of d' was 1.40 (*SE* = 0.16) for the Los Angeles sample and 2.17 (*SE* = 0.14) for the New York City sample.

Table 3. Analysis of Variance Testing the Main Effect of Age Group on Performance (d') When Participants Received Happy Cues and Were in the Neutral State

Effect	*df*	*F*	*p*	η_p^2
Main effects				
Age group	2, 98	10.90	< .001	.149
Sex	1, 98	1.49	.226	.024
Site	1, 98	18.29	< .001	.163
Interactions				
Age Group × Sex	2, 98	1.74	.181	.039
Age Group × Site	2, 98	0.34	> .250	.006
Sex × Site	1, 98	2.13	.148	.021
Age Group × Sex × Site	2, 98	0.30	> .250	.006

Note: The mean value of d' was 1.29 (*SE* = 0.19) for teens, 1.94 (*SE* = 0.18) for young adults, and 2.42 (*SE* = 0.20) for adults. The mean value of d' was 1.24 (*SE* = 0.20) for the Los Angeles sample and 2.22 (*SE* = 0.12) for the New York City sample.

Table 4. Analysis of Variance Testing the Main Effect of Age Group on Performance (d') When Participants Were in the Threat State and Received Neutral Cues

Effect	*df*	*F*	*p*	η_p^2
Main effects				
Age group	2, 98	17.57	< .001	.237
Sex	1, 98	0.32	> .250	.001
Site	1, 98	7.70	.007	.076
Interactions				
Age Group × Sex	2, 98	0.88	> .250	.020
Age Group × Site	2, 98	0.41	> .250	.008
Sex × Site	1, 98	0.36	> .250	.004
Age Group × Sex × Site	2, 98	0.05	> .250	.001

Note: The mean value of d' was 1.66 (*SE* = 0.16) for teens, 2.39 (*SE* = 0.16) for young adults, and 3.15 (*SE* = 0.23) for adults. The mean value of d' was 1.67 (*SE* = 0.17) for the Los Angeles sample and 2.64 (*SE* = 0.15) for the New York City sample.

Table 5. Analysis of Variance Testing the Main Effect of Age Group on Performance (d') When Participants Were in the Excitement State and Received Neutral Cues

Effect	*df*	*F*	*p*	η_p^2
Main effects				
Age group	2, 98	8.65	< .001	.131
Sex	1, 98	0.00	> .250	.000
Site	1, 98	5.74	.018	.058
Interactions				
Age Group × Sex	2, 98	1.18	> .250	.022
Age Group × Site	2, 98	1.23	> .250	.026
Sex × Site	1, 98	0.57	> .250	.006
Age Group × Sex × Site	2, 98	0.18	> .250	.004

Note: The mean value of d' was 2.17 (*SE* = 0.16) for teens, 2.67 (*SE* = 0.23) for young adults, and 3.32 (*SE* = 0.22) for adults. The mean value of d' was 2.27 (*SE* = 0.16) for the Los Angeles sample and 2.94 (*SE* = 0.16) for the New York City sample.

Table 6. Analysis of Variance Testing the Main Effect of Age Group on Performance (d') in the Control Condition (Neutral State and Neutral Cues)

Effect	*df*	*F*	*p*	η_p^2
Main effects				
Age group	2, 98	7.81	< .001	.104
Sex	1, 98	0.01	> .250	.000
Site	1, 98	17.02	< .001	.150
Interactions				
Age Group × Sex	2, 98	1.27	> .250	.026
Age Group × Site	2, 98	0.47	> .250	.011
Sex × Site	1, 98	1.97	.164	.020
Age Group × Sex × Site	2, 98	0.78	> .250	.016

Note: The mean value of d' was 1.80 (*SE* = 0.18) for teens, 2.36 (*SE* = 0.20) for young adults, and 2.84 (*SE* = 0.23) for adults. The mean value of d' was 1.89 (*SE* = 0.15) for the Los Angeles sample and 2.69 (*SE* = 0.16) for the New York City sample.

Table 7. Main Effects and Interactions for the Full Experimental Design

Effect	*df*	*F*	*p*	η_p^2
Main effects				
State	2, 196	47.59	< .001	.477
Cue type	2, 196	29.23	< .001	.371
Age group	2, 98	15.09	< .001	.200
Sex	1, 98	0.26	> .250	.007
Site	1, 98	20.49	< .001	.177
Interactions				
State × Cue Type	4, 392	3.82	.005	.143
State × Age Group	4, 196	1.58	.181	.022
State × Sex	2, 196	0.30	> .250	.008
State × Site	2, 196	4.00	.020	.063
Cue Type × Age Group	4, 196	2.99	.020	.053
Cue Type × Sex	2, 196	1.71	.183	.030
Cue Type × Site	2, 196	0.99	> .250	.020
Age Group × Sex	2, 98	0.95	> .250	.022
Age Group × Site	2, 98	0.25	> .250	.006
Sex × Site	1, 98	3.05	.084	.030
State × Cue Type × Age Group	8, 392	1.39	.199	.066
State × Cue Type × Sex	4, 392	1.18	> .250	.051
State × Cue Type × Site	4, 392	5.64	< .001	.169
State × Age Group × Sex	4, 196	0.37	> .250	.008
State × Age Group × Site	4, 196	1.73	.145	.031
State × Sex × Site	2, 196	0.07	> .250	.002
Cue Type × Age Group × Sex	4, 196	0.33	> .250	.007
Cue Type × Age Group × Site	4, 196	0.86	> .250	.018
Cue Type × Sex × Site	2, 196	0.36	> .250	.007
Age Group × Sex × Site	2, 98	0.46	> .250	.009
State × Cue Type × Age Group × Sex	8, 392	1.76	.084	.070
State × Cue Type × Age Group × Site	8, 392	2.44	.014	.087
State × Cue Type × Sex × Site	4, 392	0.66	> .250	.031
State × Age Group × Sex × Site	4, 196	0.76	> .250	.017
Cue Type × Age Group × Sex × Site	4, 196	0.75	> .250	.014
State × Cue Type × Age Group × Sex × Site	8, 392	0.36	> .250	.012

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